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☐	L14	L13	1130
☐	L13	L12 and lysate	1130
☐	L12	L11 and kit	1743
☐	L11	L10 and leishmania	2625
☐	L10	L9 and l8	646160
☐	L9	skin test	1890731
☐	L8	dextran free	3145409
☐	L7	L6 and pressure	316
☐	L6	L5 and diagnosis	400
☐	L5	L4 and lysate	522
☐	L4	L3 and phenol	659
☐	L3	L2 and free	1313
☐	L2	L1 and dextran	1396
☐	L1	leishmania	3803

END OF SEARCH HISTORY

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L15: Entry 27 of 71 File: PGPB Nov 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020169285
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020169285 A1

TITLE: Leishmania antigens for use in the therapy and diagnosis of leishmaniasis

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reed, Steven G.			US	
Campos-Neto, Antonio			US	
Webb, John R.			US	
Dillon, David C.			US	

US-CL-CURRENT: 530/350

CLAIMS:

1. An isolated polypeptide comprising an immunogenic portion of a Leishmania antigen or a variant thereof, wherein said antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 4, 20, 22, 24, 26, 36-38, 41, 50-53, 82, 104, 106, 108, 110, 112, 118-122, 134 and 135, and variants thereof.

2. An isolated antigenic epitope of a Leishmania antigen comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: 43, 56, 57 or 58.

3. An isolated polypeptide comprising at least two contiguous antigenic epitopes according to claim 2.

4. An isolated polynucleotide comprising a DNA sequence encoding a polypeptide according to any one of claims 1 and 3.

5. The polynucleotide of claim 4, wherein the DNA sequence is selected from the group consisting of: SEQ ID NO: 1, 3, 19, 21, 23, 25, 29-31, 34, 45-48, 74, 102, 103, 105, 107, 109, 111, 113-117 and 129-133.

6. A recombinant expression vector comprising a polynucleotide according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of E. coli, yeast and mammalian cells.

9. A fusion protein comprising at least two polypeptides according to any one of claims 1 and 3.

10. A fusion protein comprising at least two antigenic epitopes according to claim 2.

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11. A pharmaceutical composition comprising a polypeptide according to any one of claims 1 and 3, and a physiologically acceptable carrier.

12. A pharmaceutical composition comprising a fusion protein according to any one of claims 9 and 10, and a physiologically acceptable carrier

13. An immunogenic composition comprising a polypeptide according to any one of claims 1 and 3 and an immunostimulant.

14. An immunogenic composition according to claim 13 further comprising a delivery vehicle.

15. The immunogenic composition of claim 14, wherein the delivery vehicle is a biodegradable microsphere.

16. An immunogenic composition comprising a polynucleotide according to claim 4 and an immunostimulant.

17. An immunogenic composition comprising a fusion protein according to any one of claims 9 and 10 and an immunostimulant

18. A method for inducing protective immunity against leishmaniasis in a patient comprising administering a pharmaceutical composition according to any one of claims 11 and 12.

19. A method for inducing protective immunity against leishmaniasis in a patient comprising administering an immunogenic composition according to any one of claims 13, 16 and 17.

20. A method for detecting Leishmania infection in a patient, comprising: (a) contacting dermal cells of the patient with a pharmaceutical composition according to any one of claims 11 and 12; and (b) detecting an immune response on the patient's skin.

21. The method of claim 20, wherein the immune response is induration.

22. A diagnostic kit comprising: (a) a pharmaceutical composition according to any one of claim 11 and 12; and (b) apparatus sufficient to contact dermal cells of a patient with the pharmaceutical composition.

23. The composition of claim 17, wherein the immunostimulant is selected from the group consisting of: aminoalkyl glucosaminide 4-phosphates; monophosphoryl lipid A; and 3-de-O-acylated monophosphoryl lipid A.

Previous Doc Next Doc Go to Doc#

L15: Entry 27 of 71 File: PGPB Nov 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020169285
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020169285 A1

TITLE: Leishmania antigens for use in the therapy and diagnosis of leishmaniasis

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reed, Steven G.			US	
Campos-Neto, Antonio			US	
Webb, John R.			US	
Dillon, David C.			US	

APPL-NO: 09/ 991496 [PALM]
DATE FILED: November 20, 2001

RELATED-US-APPL-DATA:
Application 09/991496 is a continuation-in-part-of US application 09/874923, filed June 4, 2001, PENDING
Application 09/874923 is a continuation-in-part-of US application 09/639206, filed August 14, 2000, PENDING
Application 09/639206 is a continuation-in-part-of US application 09/565501, filed May 5, 2000, PENDING
Application 09/565501 is a continuation-in-part-of US application 09/551974, filed April 14, 2000, PENDING
Application 09/551974 is a continuation-in-part-of US application 09/183861, filed October 30, 1998, US Patent No. 6365165
Application 09/183861 is a continuation-in-part-of US application 09/022765, filed February 12, 1998, US Patent No. 6375955
Application 09/022765 is a continuation-in-part-of US application 08/920609, filed August 27, 1997, PENDING
Application 08/920609 is a continuation-in-part-of US application 08/798841, filed February 12, 1997, PENDING
Application 08/798841 is a continuation-in-part-of US application 08/533669, filed September 22, 1995, US Patent No. 5834592

INT-CL: [07] C07 K 1/00, C07 K 14/00, C07 K 17/00

US-CL-PUBLISHED: 530/350
US-CL-CURRENT: 530/350

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

Compositions and methods for preventing, treating and detecting leishmaniasis and stimulating immune responses in patients are disclosed. The compounds provided include polypeptides that contain at least an immunogenic portion of one or more

Leishmania antigens, or a variant thereof. Vaccines and pharmaceutical compositions comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided and may be used, for example, for the prevention and therapy of leishmaniasis, as well as for the detection of Leishmania infection.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/874,923 filed Jun. 4, 2001, which is a continuation-in-part of U.S. patent application Ser. No. 09/639,206 filed Aug. 14, 2000, which is a continuation-in-part of U.S. patent application Ser. No. 09/565,501 filed May 5, 2000, which is a continuation-in-part of U.S. patent application Ser. No. 09/551,974 filed Apr. 14, 2000, which is a continuation-in-part of U.S. patent application Ser. No. 09/183,861, filed Oct. 30, 1998 (allowed), which is a continuation in part of U.S. patent application Ser. No. 09/022,765, filed Feb. 12, 1998 (allowed), which is a continuation-in-part of U.S. patent application Ser. No. 08/920,609, filed Aug. 27, 1997, which is a continuation-in-pan of U.S. patent application Ser. No. 08/798,841, filed Feb. 12, 1997, which is a continuation-in-part of U.S. patent application Ser. No. 08/533,669, filed Sep. 22, 1995, now U.S. Pat. No. 5,834,592, and are incorporated in their entirety herein by reference.

Previous Doc Next Doc Go to Doc#

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L15: Entry 63 of 71 File: USPT Nov 10, 1998

US-PAT-NO: 5834592
DOCUMENT-IDENTIFIER: US 5834592 A

TITLE: Leishmania antigens for use in the therapy and diagnosis of Leishmaniasis

DATE-ISSUED: November 10, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Reed; Steven G.	King	WA		
Campos-Neto; Antonio	King	WA		
Webb; John R.	King	WA		
Dillon; Davin C.	King	WA		
Skeiky; Yasir A. W.	King	WA		

US-CL-CURRENT: 530/350; 424/184.1, 424/269.1, 530/364, 530/806, 930/210

CLAIMS:

We claim:

1. An isolated polypeptide comprising an immunogenic portion of a Leishmania antigen having the amino acid sequence recited in SEQ ID NO: 4, or a variant of said antigen that differs only in conservative substitutions, modifications or combinations thereof.

2. The polypeptide of claim 1, comprising amino acids 1-175 of SEQ ID NO:4.

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L15: Entry 22 of 71 File: PGPB Apr 17, 2003

PGPUB-DOCUMENT-NUMBER: 20030072714
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030072714 A1

TITLE: Microfluidized leishmania lysate and methods of making and using thereof

PUBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Magill, Alan J.	Kensington	MD	US	
Stiteler, John M.	Springfield	VA	US	
Grogl, Max	Columbia	MD	US	
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Eckels, Kenneth H.	College Park	MD	US	
Ballou, William R.	Silver Spring	MD	US	

APPL-NO: 09/ 975020 [PALM]
DATE FILED: October 12, 2001

INT-CL: [07] A61 K 49/00, G01 N 33/53, G01 N 33/569

current appl

US-CL-PUBLISHED: 424/9.81; 435/7.22
US-CL-CURRENT: 424/9.81; 435/7.22

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

Disclosed herein are microfluidized lysate preparations of Leishmania parasites and methods of making thereof. Also disclosed are methods of using the microfluidized lysate preparations in skin test antigen assays as well as kits comprising the microfluidized lysate preparations. The microfluidized lysate preparations are made under current good manufacturing practice and may therefore be standardized and such preparations may be produced with consistently.

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L15: Entry 12 of 71 File: PGPB Jan 8, 2004

PGPUB-DOCUMENT-NUMBER: 20040005326
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040005326 A1

TITLE: Leishmania vaccine

PUBLICATION-DATE: January 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mottram, Jeremy Charles	Bearsden		GB	
Coombs, Graham Herbert	Glasgow		GB	

US-CL-CURRENT: 424/184.1

CLAIMS:

1. Use of a mutant Leishmania in the preparation of a vaccine, wherein the mutant Leishmania comprises at least one defective cysteine proteinase gene type, such that the mutant Leishmania is substantially incapable of expressing a functionally active form of said at least one cysteine proteinase.

2. Use of a mutant Leishmania according to claim 1 wherein the mutant Leishmania comprises two or more defective cysteine proteinases.

3. A vaccine formulation comprising a mutant Leishmania, said mutant Leishmania comprising at least one defective cysteine proteinase gene type, such that the mutant Leishmania is substantially incapable of expressing a functionally active form of said at least one cysteine proteinase.

4. A vaccine formulation according to claim 3 wherein the mutant Leishmania comprises two or more defective cysteine proteinases.

5. A vaccine formulation according to either of claims 3 or 4 wherein the mutant Leishmania is selected from any species of Leishmania including L. braziliensis, L. peruviana, L. guyanensis, L. mexicana, L. major, L. amazonensis, L. infantum, L. chagasi and L. donovani.

6. A vaccine formulation according to claim 5 wherein the mutant Leishmania is a L. mexicana mutant and said defective cysteine proteinase gene(s) is/are selected from cpa, cpb and/or cpc.

7. A vaccine formulation according to claim 6 wherein the L. mexicana mutant is a cpb single null mutant.

8. A vaccine formulation according to claim 6 wherein the L. mexicana mutant is a cda/cpb double null mutant.

9. A vaccine formulation according to claim 5 wherein the mutant Leishmania is a L. infantum mutant and said defective proteinase gene(s) is/are selected from cpa and/or cpb.

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10. A vaccine formulation according to claim 9 wherein the L. infantum cpa is identifiable from the sequence shown in FIG. 8 and/or the cpb is identifiable from the sequence as shown in FIG. 10.

11. A vaccine formulation according to any preceding claim wherein the cysteine proteinase gene has been modified by a deletion, insertion, substitution or rearrangement such that said cysteine proteinase gene(s) is/are substantially incapable of expressing a functionally competent cysteine proteinase.

12. A vaccine formulation according to claim 11 wherein said cysteine proteinase gene has been modified by deletion of all or a portion of said cysteine proteinase gene.

13. A vaccine formulation according to claim 12 wherein a gene or gene fragment capable of expressing a polypeptide selected from polypeptides which augment an immune response and marker polypeptides is inserted with a gap generated by deletion of all or the portion of said cysteine proteinase gene.

14. A vaccine formulation according to claim 13 wherein the polypeptide is a cytokine.

15. A vaccine formulation according to claim 13 wherein at least one copy of said cysteine proteinase gene has been modified such that a substantially inactive form of a cysteine proteinase polypeptide is expressed.

16. A vaccine formulation according to any preceding claim wherein the mutant Leishmania is a drug resistant marker-free mutant.

17. A vaccine formulation according to any preceding claim for eliciting at least a cellular immune response.

18. A vaccine formulation according to claim 17 wherein the cellular immune response is a Th1 cell response.

19. A vaccine formulation according to any preceding claim further comprising an adjuvant and/or cytokine.

20. A vaccine formulation according to any preceding claim further comprising at least one disfunctional cysteine proteinase, wherein said disfunctional cysteine proteinase is substantially enzymatically inactive, but which is antigenic or immunogenic.

21. A method of vaccinating against Leishmania which comprises administering to an animal an effective, non-toxic amount of a vaccine formulation according to any one of claims 3-20.

22. A method according to claim. 21 wherein the method comprises parenteral administration.

23. Use of a mutant Leishmania in the manufacture of a vaccine for the prophylaxis and/or treatment of Leishmaniasis, wherein the mutant comprises at least one defective cysteine proteinase gene type, such that the mutant Leishmania is substantially incapable of expressing a functionally active form of said at least one cysteine proteinase.

24. A pharmaceutical formulation comprising a vaccine according to any one of claims 3-20 together with a carrier or excipient.

Previous Doc Next Doc Go to Doc#

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L15: Entry 30 of 71 File: PGPB Mar 7, 2002

DOCUMENT-IDENTIFIER: US 20020028215 A1
TITLE: NOVEL VACCINES AND PHARMACEUTICAL COMPOSITIONS USING MEMBRANE VESICLES OF MICROORGANISMS, AND METHODS FOR PREPARING SAME

Summary of Invention Paragraph:
[0004] Conventional prophylactic treatments for infectious diseases are also becoming increasingly ineffective with the emergence of resistant mutant strains of infectious agents. Vaccines for the prophylaxis of infectious diseases have been developed which incorporate whole attenuated organisms, cell lysates, culture supernatants or extracts of the infectious agents. There has been considerable interest in improving existing vaccines since they typically contain fractions having physical or chemical characteristics which result in toxicity or undesired immune responses.

Summary of Invention Paragraph:
[0015] The invention also provides a method for screening for an immunogenic antigen of a pathogen comprising (a) providing a membrane vesicle having a test antigen associated with its surface; (b) vaccinating an animal with the membrane vesicle; and (c) challenging the animal with the pathogen to determine if the test antigen provides protection against the pathogen.

Detail Description Paragraph:
[0069] The microorganisms which produce membrane vesicles described herein may also be transfected with one or more nucleotide sequences encoding exogenous proteins in order to provide membrane vesicles have exogenous proteins incorporated into the membrane vesicles or associated with their surface. For example, the exogenous proteins include antigens which are associated with infectious diseases caused by infectious agents which do not produce membrane vesicles including viruses such as human immunodeficiency virus (HIV), influenza (nuriminidase/haemagglutinin), adenovirus, Herpes simplex, measles, simian immunodeficiency virus; fungi such as Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatidis, Candida albicans; protozoa such as Leishmania mexicana, Plasmodium falciparum and Taxoplasma gondii; and, gram-positive bacteria such as Streptococcus mutans, and S. pneumoniae (cell wall antigens). Microorganisms transfected with such antigens may be used to produce membrane vesicles which may be used as vaccines against the infectious agent. The microorganism may also be transfected with a nucleotide sequence encoding an exogenous protein having a known therapeutic or regulatory activity such as hormones preferably insulin, blood clotting factor VIII, growth hormones, hirudin, cytokines such as gamma interferon, tumor necrosis factor, IL-1, IL-2,IL-3, I1-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, GM-CSF, CSF-1, and G-CSF. Membrane vesicles containing therapeutic or regulatory proteins may be used to deliver the proteins to a host. The microorganisms may also be transfected with proteins which facilitate targeting of a membrane vesicle having the proteins associated with their surfaces to specific target tissues or cells. For example, tumor-associated antigens, CD.sub.4 proteins on T-helper cells, and gp120 in HIV.

Detail Description Paragraph:
[0090] In accordance with another embodiment of the invention, a vaccine against infectious diseases caused by an infectious agent which does not produce membrane vesicles is provided which comprises a carrier strain having a membrane vesicle from a microorganism integrated into the cell surface of the carrier strain, wherein the membrane vesicle has an amount of an antigen associated with its surface which is effective to provide protection against the infectious agent. The vaccines may be used for the prophylaxis or active immunization and treatment of

infectious diseases caused by microorganisms including viruses such as human immunodeficiency virus (HIV), influenza (nuriminidase/haemagglutinin), adenovirus, Herpes simplex, measles, simian immunodeficiency virus; fungi such as Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatidis, Candida albicans; protozoa such as Leishmania mexicana, Plasmodium falciparum and Taxoplasma gondii; and, gram-positive bacteria such as Streptococcus mutans, and S. pneumoniae. Therefore, the vaccines of the present invention may incorporate membrane vesicles with immunogenic antigens of these microorganisms.

Detail Description Paragraph:
[0114] Administration of an amount effective to have a bactericidal effect is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example, an amount effective to have a bactericidal effect may vary according to factors such as the disease state, age, sex, and weight of the individual. Dosage regimes may be adjusted to provide the optimum therapeutic response. Amounts of membrane vesicles effective to have a bactericidal effect on a selected gram-negative and/ or gram-positive bacterial pathogen may be determined using conventional in vivo and in vitro tests (see zymogram systems as outlined in Bernadsky, G. et al. supra).

Detail Description Paragraph:
[0159] The invention also relates to a method of inserting nucleic acid molecules into a target cell which comprises encapsulating the nucleic acid in a membrane vesicle of a microorganism, and bringing the membrane vesicle in contact with the target cell whereby the nucleic acid molecule is inserted into the cell. Nucleic acid molecules which may be encapsulated in a membrane vesicle may be from eucaryotic or prokaryotic cells and they may be endogenous or exogenous to a microorganism that produces membrane vesicles. Examples of nucleic acid molecules which may be encapsulated in a membrane vesicle are nucleic acid molecules encoding (a) mammalian proteins such as hormones preferably insulin, blood clotting factor VIII, growth hormones, hirudin, cytokines, and a normal copy of the cystic fibrosis transmembrane conductance regulator (CFTR); (b) viral antigens such as HIV glycoprotein, hepatitis B surface antigens, influenza antigens; fungal antigens for example from Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatidis, Candida albicans; and (c) protozoal antigens for example from Leishmania mexicana, Plasmodium falciparum and Taxoplasma gondii.

Detail Description Paragraph:
[0169] Antibiotic Susceptibility Test.

Detail Description Paragraph:
[0176] Proteinases were resolved by SDS-PAGE using the method of Matsumoto et. al. (Invest. Opthalmol. Vis. Sci. 34:1945-1953, 1993) with slight modifications. The separating gels used were 8% SDS gels containing a-casin or gelatin (Type A from bovine skin; Sigma) at a final concentration of 0.15%. The stacking gels consisted of 4% SDS gels without gelatin or casein. A 25 .mu.g protein sample from each preparation (without reducing agents) was loaded onto gels and was run at 4.degree. C. for 90 min. at 120 V. After electrophoresis, the gels were shaken at room temperature in a solution of 2.5% Triton-X100 for 45 min. to remove the SDS. Subsequently, the gels were incubated at 37.degree. C. in incubation buffer (50 mM Tris-HCl, pH 8.0, 5 mM CaCl.sub.2) with 5 mM EDTA for 18 h. The positions of the proteinases were identified after the gels were stained (0.5% Comassie brilliant blue R-250, 10% acetic acid, 40% methanol) for 2 h and clear bands were identified.

Detail Description Paragraph:
[0180] The DNA content in MVs was quantitated using an assay developed by the Pierce Chem. Co. (Pierce, Rockford, Ill.) according to the manufacturer's instructions. Briefly, 20 .mu.g of protein from MVs in 50 .mu.l assay buffer (0.1 M NaCI, 10 mM EDTA, 10 mM Tris, pH 7.0) was lysed with 50 .mu.l of extraction solution (0.1 M NH.sub.4OH, 0.2% Triton X-100). A standard curve for DNA was prepared with calf thymus DNA (0-150 ng/ml) (provided with the assay kit) in 200 mM NaCI, 20 mM EDTA, pH 7.0, 0.05 NH.sub.4OH, 0.01% Triton X-100). To each sample, 1.5 ml of fluorescent dye (200 .mu.g/ml) (Bisbenzimidazole) was added, the tubes

were capped quickly, mixed and fluorescence was measured in a Hitachi F-2000 fluorescence spectrophotometer with excitation and emission wave lengths set at 350 and 455 nm, respectively (10-nm slit width), and yielded values for total DNA/mg of protein Experiments were also performed on MVs without their being treated with extraction solution. For some experiments, the intact MVs and purified DNA were treated with pancreatic DNase 1 (1.0g/ml; Sigma).

Detail Description Paragraph:
[0181] Preparation of Cell Lysates, Supernatants and MVs for Enzyme Assays.

Detail Description Paragraph:
[0182] Membrane-filtered supernatants, before and after harvesting MVs, were concentrated 10-fold in a Concentrator evaporator jouan, Winchester, Va.). Washed whole cells or MVs, were sonicated for 2 min. with 0.1 % v/v toluene to release intracellular enzymes in a sonic bath (Bransonic Ultrasonic Corporation,Ianburg, Conn.). Protein concentrations of samples were determined with the micro BCA reagent kit (Pierce). Whole cells and MVs (both at a 20 .mu.g protein concentration) or concentrated supernatants (50 .mu.l) were assayed for enzyme activity.

Detail Description Paragraph:
[0189] FIG. 1 shows thin sections of H 103 cells showing the formation of vesicles (solid arrowheads) and free MVs in growth medium (open arrow); (A), Control and (B), exposed to 4.times. MIC of gentamicin. A larger number of Mvs are formed from the cell surface of bacteria exposed to gentamicin than from unreacted cells. Electron dense material has been trapped in the developing and free vesicles. Bar=100 nm.

Detail Description Paragraph:
[0190] FIG. 1 shows thin-sections of P. aeruginosa either treated with gentamicin or untreated. The untreated control cells (FIG. 1(A)) represent "natural" cultured cells and possessed intact cell envelopes, with several membrane blebs emanating from each cell surface or free in the environment. Cells that were exposed to gentamicin formed many more blebs (FIG. 1(B)) than those seen in untreated cells. At a gentamicin concentration of 8 .mu.g/ml, this increase in blebbing was visible after approximately 1 min of antibiotic incubation. Examination of intact isolated purified blebs from both natural and gentamicin-treated cultures in negative stains showed that, although they were partially collapsed, many were filled with a particulate substance (FIG. 2(A) is an electron micrograph showing a negative stain of intact gentamicin-MVs (g-MVs)). This was better shown and confirmed with thin sections (FIG. 2(B) shows an electron micrograph of a thin section of intact g-MVs). The diameter of the vesicles from both untreated and gentamicin-treated cells varied between 50 nm to 150 nm when measured in thin sections; however, when measurements of g-MVs were averaged, the g-MVs were found to be slightly larger than natural MVs (n-MVs), with a mean diameter of 100 nm as opposed to 80 nm for n-MVs. Thin sections proved the vesicles to have a bilayer structure (FIG. 2(B)). No external material was seen by any TEM technique, thereby suggesting the isolated vesicles were free from particulate cellular debris.

Detail Description Paragraph:
[0194] The protein profiles of whole cell lysates, OMPs extracted from whole cells and MVs from untreated or treated cells were compared by SDS-PAGE. FIG. 3 shows SDS-PAGE profiles of n-MV, g-MV, outer membrane proteins (OMP), and control whole cells (WCC) in a 12% polyacrylamide gel stained with Comassie brilliant blue. Each lane contains 25 .mu.g of total protein from the indicated samples. Molecular masses (in kilodaltons) are indicated on the left.

Detail Description Paragraph:
[0195] The n-MVs and g-MVs contained much fewer protein bands than the OMPs extracted from whole cells or whole cell lysates. The banding patterns of n-MVs and g-MVs were very similar, but not identical; both types of Mvs appeared to have lost several bands which were normally present in whole cell lysates and the OMP samples. Some of the prominently stained bands from both vesicle preparations included .about.70 kD, 40 kD and 20 kD proteins. Trace amounts of an -35 kD protein

was detected in g-MVs but not in n-MVs.

Detail Description Paragraph:
[0200] Tables 2 and 3 illustrate the enzymatic activities in cellular extracts, MVs and culture supenatants, from cultures which were treated with gentamicin or untreated. Both types of vesicles exhibit PLC activity, as measured spectrophotometrically by the hydrolysis of p-nitrophenylphosphrylcholine, indicating that the enzyme is associated with the MVs. To evaluate the PLC activity in the supernatants, the enzyme activity was assayed before and after the removal of vesicles from cell-free culture supenatants. Removal of vesicles from gentamicin-treated cultures resulted in an 83% reduction in enzyme activity as compared to a 68% decrease in untreated cultures (Table 3). This suggests that the majority of PLC secreted into the external environment is indeed concentrated in the vesicles. The observed difference in enzyme activity between the two cultures is due to the fact that the amount of vesicles per unit mass is greater in gentamicin-exposed cultures than in untreated cultures, hence a higher percentage of PLC activity is removed with the vesicles. It has been reported previously that P.aeruginosa produces and excretes two distinct PLCs with similar activities; each is capable of acting on the substrate, phosphatidylcholine (Shortridge, V. D. et al., Mol Microbiol. 6:863-871, 1992). Although both PLCs hydrolyse this substrate, one is hemolytic (PLC-H) for sheep and human erythrocytes and is heat labile, while the other (PLC-N) is not. Additionally, PLC-H can hydrolyse sphingomyelin, but not phosphatidylserine, whereas PLC-N hydrolyses phosphatidylserine but not sphingomyelin (Bergmann U., et al., Infect. Immun. 57:2187-2195, 1989; Berk, R. S. Infect. Immun. 55:1728-1730, 1987; and, Vasil, M. L. et al., Antibiot. Chemmnother. 44:34-47, Karger, Basel, 1991). The MVs were examined for hemolytic activity on sheep blood agar plates as well as spectrophotometrically on sheep blood cells, and it was found that both types of MVs were positive. No attempt was made to differentiate between PLC-H and PLC-N in the study.

Detail Description Paragraph:
[0202] P. aeruginosa secretes several proteases (Hastie, A., et ale, Infect. Immun. 40:506-513, 1983; Kessler, e., et al., J. Biol. Chem. 268:7503-7508; Lazdusniski, A. J., et al., Biochimie 72:147-156, 1990; and, Wretlind, B., and O. R. Pavlovskis, Rev. Infect. Dis. 5:S998-1004, 1983).The secretion of elastase and protease was examined in strain ATCC 19660 since the amounts of both enzymes produced by this strain was found to be larger than those for strain H 103. No appreciable amount of proteolytic or elastolytic activity was detected in toluene cellular extracts, indicating the lack of intracellular accumulation of active enzymes (Table 2). This observation was in agreement with earlier work (Duoung, F. et al, Gene 121:47-54, 1992; Guzzo, J., et al, J.Bacteriol. 173:5290-5297, 1991; Hamood, A.N. et al., Infect. Immun. 60:510-517, 1992; Hastie, a. et al., Infect Immun. 40:506-513, 1983; Kessler, E., et al., J. Biol. Chem. 268:7503-7508, 1993; and Lazdusniski, A. J., et al., Biochimie 72:147-156, 1990). Examination of both types of MVs for protease activity demonstrated the association of active enzyme. On removal of vesicles from cell-free culture supernatants, the total protease activity dropped by 18% in untreated culture supernatants and 25% in gentamicin-treated culture supernatants. Since an appreciable amount of activity could also be detected in culture supernatants following the removal of vesicles from cell-free medium, the enzyme is probably released from cells in both soluble and vesicle-associated forms. In contrast, elastolytic activity was detected exclusively in culture supernatants and was not affected by removal of vesicles from cell-free culture supernatants. Previous studies have demonstrated that the enzyme is secreted as a proenzyme that becomes active only as it is released into the supernatant (Guzzo, J. et al., J. Bacteriol. 173:5290-5297, 1991; and Kessler, E. et al., J Biol. Chem. 268:7503-7508, 1993). For this reason, even if the proenzyme is present in MVs, it would not be detectable by its enzyme activity.

Detail Description Paragraph:
[0208] As judged by the location of gold particles on thin sections, a uniform distribution of the enzyme in the cytoplasm is clearly seen. Interestingly, it can also be seen that cytoplasm is streaming into a forming vesicle. Budding and free vesicles were labelled to the same extent with gold particles, demonstrating that PLC is entrapped within both types of Mvs. This was in good agreement with the

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biochemical demonstration of the enzyme activity in vesicle preparations (Tables 2 and 3). Immunogold labelling for the localization of alkaline phosphatase in thin-sections of intact cells and Mvs demonstrated that the majority of the enzyme was located in the envelope, particularly in the periplasm and outer membrane (FIG. 7). MVs were labelled on the membrane and on the luminal material attached to the membrane. g-MVs and n-MVs were labelled to approximately the same extent, confirming the result of the enzymatic assay (Table 2).

Detail Description Paragraph:
[0212] In particular, FIG. 9 shows Western immunoblot analysis of samples with antibodies to (A) elastase and (B) alkaline protease. Whole cell extracts from untreated control cells (WCC) or gentamicin-treated cells (WCG), n-MVs and g-MVs and cell-free supernatants after removal of MVs from untreated (n-sup) or gentamicin-treated (g-sup) cultures are shown. Lane P, contained purified elastase. Each lane contains 25 .mu.g of protein or 10 .mu.l of concentrated n-sup or g-sup. FIG. 9(C) shows proteinase present in MVs tested by gelatin zymography. Both n-MVs and g-MVs demonstrated three major bands (M.sub.r.about.33, 35 and 135 kDa) having proteolytic activity. Molecular masses (in kilodaltons) are indicated of the left and right.

Detail Description Paragraph:
[0218] Because the Mvs were isolated from early stationary phase growth cultures, it was also possible that some of the DNA was derived from lysed cells (within each culture) which had bound to the outer face of the vesicles. This could especially be true of g-MVs. Control experiments conducted with exhaustive treatment of MVs with pancreatic DNase showed that this was not the case. DNase-treated n- and g-MVs possessed amounts of DNA similar to those in Table 4. These control experiments also confirmed that the MVs were intact, since the DNA of the MVs was protected from the external enzyme. When in similar experiments containing Mvs and free DNA were treated with pancreatic DNase, and ethidium-bromide gel electrophoresis was performed, the external DNA was shown to be digested whereas the MV DNA remained intact.

Detail Description Paragraph:
[0308] In the P. aeruginosa system, although most extracellular autolytic activity is associated with MVs, some soluble activity can also be demonstrated. Therefore, once MVs are removed from the spent culture medium, there is still some residual peptidoglycan degrading activity. If E. coli is incubated with this spent liquor or the MVs lysate, there is no drop in viability indicated that the bacterium's outer membrane is an impermeable barrier to the soluble autolysins, this emphasizes the importance of the MV's bilayered membrane in directly entrapped autolysins to the E. coli (or other gram-negative) peptidoglycan layer. Once the MVs adhere to the outer membrane, the MV's membrane and outer membrane must fuse together, emptying the MV luminal contents into the host periplasm where the P. aeruginosa autolysins hydrolyse the peptidoglycan layer of intact cell.

Detail Description Paragraph:
[0312] The effect of n-MVs, g-MVs and gentamicin (2.5.times.MIC of antibiotic for gentamicin sensitive strains or 100 .mu.g/ml of gentamicin for the 8803 strain) on the viability of D.sub.2C, DH5.alpha., PAO1, and 8803 is shown in FIG. 23. P. aeruginosa PAO1 is the parent strain from which the MVs are derived. It was exquisitely sensitive to both g-MVs and the free gentamicin at 2.5 MIC. There was a small but discernable loss of viability of S. aureus, E. coli and P. aeruginosa PAO1 (FIGS. 23(a), (b) and (c) exposed to n-MVs. Even though peptidoglycan hydrolysis must have occurred (FIGS. 19 and 20), the loss in viability was less than expected. DH5.alpha. and PAO1 remained at a constant cell number for the first 1-2 h, and this gradually increased by 5 h. The n-MV cell numbers were only slightly reduced to those of the control cultures. The small effect of n-MVs on these cultures was presumably due to a rapid replacement of lysed cells with newly divided cells or to a rapid replacement of hydrolyzed peptidoglycan with newly synthesized polymer so that lysis was inhibited.

Detail Description Paragraph:
[0335] Mouse Immunization: Six-to seven week old female BALB/c mice (in groups of

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six) were immunized orally via a gavage tube, with 0.3 ml of one of the following test vaccines: (i) Ty21a (2 x 10.sup.8 CFU/ml); (ii) PAO1 MVs (100 .mu.g protein/ml); (iii) M90T MVs (100 fig protein/ml); (iv) Ty21a (2.times.10.sup.8 CFU/ml)+M90T MVs (at 100 .mu.g protein/ml) (v) Ty21a (2.times.10.sup.8 CFU/ml)+PAO1 MVs (100 .mu.g/ml); (vi) Ty21a (2.times.10.sup.8 CFU/ml)+PAO1 MVs+M90T MVs (at 100 .mu.g protein/ml); and, (vii) a control group with 0.3 ml sterile PBS. All vaccines were suspended immediately before immunization in 3% NaHCO.sub.3 in PBS at pH 8.0, and given four times at one week intervals. One week after the final immunization, mice were sacrificed, bled and the serum was collected. Bronchoalveolar washings were obtained as described in Guzman, C. A. et al, 1991, Infect. Immun. 59:4391-4397. Briefly, trachea and lungs were aspirated with 2.0 ml of ice-cold PBS containing 2 mM phenylmethylsulfonylfluoride (PBSPMSF as a protease inhibitor) (Sigma Chemical Co., St. Louis, Mo.), three times to get an even distribution of the solution between each lung, before collecting the final fluid having a volume of 0.6-0.8 ml. Gut washes were obtained by washing the complete gut segment which was distal from the stomach with 1.5 ml ice-cold PBS-PMSF. The washings were centrifuged at 3000 x g for 10 min. at 4.degree. C. to remove cellular debris and stored at -20.degree. C. until tested.

Detail Description Paragraph:
[0341] By electron microscopy of thin sections isolated, purified MVs from S.flexneri strain M90T and P. aeruginosa stain PAO1 were bilayered spherical vesicles ca. 80 nm in diameter and (most) were filled with a particulate substance. The protein profiles of whole cell lysates, OMPs (extracted for whole cells), and MVs from M90T and PAO1 were compared by SDS-PAGE (FIG. 24(a)). The banding patterns of M90T MVs were similar, but not identical, to the corresponding OMPs from whole cells; the major .about.35 and 37 kDa. The prominently stained MV bands from PAO1 included .about.-45 and 55-kDa proteins which were also prominent in the whole cell OMP fraction.

Detail Description Paragraph:
[0347] Serum or mucosal samples in which specific immunoglobulins could be detected by ELISA were next analysed by Western blotting to determine whether the induced antibodies were directed against LPS or protein antigens (FIG. 27). Samples were analysed for serum IgA, IgG and IgM and mucosal IgA with sample buffer or proteinase-K treated M90T or PAO1 whole cells as the antigen. Proteinase-K treatment was used to de-proteinize the antigenic samples so that those antibodies directed against LPS in the body fluid could more easily be detected. Strong anti-LPS antibodies were evident for both M90T and PAO1-specific LPS. The IgA, IgG, and IgM responses to the various vaccine constructs showed a similar trend to that previously seen in ELISA tests. The antibody response to M90T MVs was weak with barely detectable bands on Western blots (FIG. 26). Immunoblotting of non-deproteinized samples with serum, lung, or gut washes revealed several immunoreactive protein-specific antibody responses (arrows) to the PAO1 (FIG. 27(b) and M90T (FIG. 27(d)) vaccine constructs. The reactivity of immunoglobulin classes to the various vaccine constructs was similar to the ELISA results. On these immunoblots, the LPS-specific antibody response was also visible for both PAO1 and M90T and, in fact, dominated the protein responses when the two overlapped. The spacing and banding patterns were more extensive and complicated in these immunoblots than those treated with proteinase-K implying that the immune response is to both LPS and protein antigens. The antibody response to the prominent 35-37kDa and 45-55 kDa protein bands of M90T and PAO1 (FIG. 24(a)) became evident when LPS-specific antibodies were removed from body fluids by adsorbing them out with either M90T or PAO1 LPS. The antibody response to the carrier strain, Ty21a, was mainly protein-spedfic (FIG. 27(d)). This was to be expected, since the growth conditions employed did not promote complex side chain LPS expression in Ty21a.

Detail Description Table CWU:
3TABLE 3 Enzyme activities in cell-free culture supernatants following the removal of MVs. % Activity remaining in cell-free supernatant after removal of MVs Enzyme n-MV g-MV PLC 32 .+-. 8 17 .+-. 5 Alk. phosphatase 49 .+-. 7 52 .+-. 6 Elastase 98 .+-. 0.8 98 0.9 Protease 82 .+-. 1.9 75 .+-. 4 abbreviations as in Table 2.

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L15: Entry 36 of 71 File: USPT Oct 28, 2003

US-PAT-NO: 6638517
DOCUMENT-IDENTIFIER: US 6638517 B2

TITLE: Leishmania antigens for use in the therapy and diagnosis of leishmaniasis

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

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Probst; Peter	Seattle	WA		
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US-CL-CURRENT: 424/269.1; 424/184.1, 424/191.1, 424/192.1, 424/265.1, 424/450, 424/85.2, 435/69.7, 514/12, 514/2, 514/44 , 530/300, 530/350, 536/23.1, 536/23.4

CLAIMS:

What is claimed is:

1. A method for inducing protective immunity against leishmaniasis in a patient comprising administering an immunogenic composition comprising a fusion protein and an immunostimulant, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO:24.

2. The method of claim 1, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO:95.

3. The method of any one of claims 1 and 2, wherein the immunostimulant is selected from the group consisting of: aminoalkyl glucosaminide 4-phosphates; monophosphoryl lipid A; and 3-de-O-acylated monophosphoryl lipid A.

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L15: Entry 38 of 71 File: USPT Aug 19, 2003

US-PAT-NO: 6607731
DOCUMENT-IDENTIFIER: US 6607731 B1

TITLE: Léishmania antigens for use in the therapy and diagnosis of leishmaniasis

DATE-ISSUED: August 19, 2003

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/269.1; 424/184.1, 424/185.1, 424/191.1, 424/192.1, 424/265.1, 514/12, 514/2, 514/46, 530/300, 530/350 , 536/23.1, 536/23.4

CLAIMS:

What is claimed is:

1. A fusion protein comprising the amino acid sequence of SEQ ID NO:24.

2. A fusion protein comprising an immunogenic portion of SEQ ID NO:24, wherein said immunogenic portion selectively binds to anti-Leishmania antibodies specific for SEQ ID NO: 24.

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L15: Entry 51 of 71 File: USPT Apr 23, 2002

US-PAT-NO: 6375955
DOCUMENT-IDENTIFIER: US 6375955 B1

TITLE: Leishmania antigens for use in the therapy and diagnosis of leishmaniasis

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

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Probst; Peter	Seattle	WA		

US-CL-CURRENT: 424/269.1; 424/184.1, 424/265.1, 530/300, 530/350, 930/210

CLAIMS:

What is claimed is:

1. An isolated polypeptide comprising an immunogenic portion of a Leishmania antigen, wherein said antigen comprises an amino acid sequence of SEQ ID NO: 82.

2. A pharmaceutical composition comprising a polypeptide according to claim 1, and a physiologically acceptable carrier, wherein the polypeptide is present in an amount effective for the treatment of Leishmaniasis.

3. A pharmaceutical composition according to claim 2, further comprising soluble Leishmania antigens.

4. A pharmaceutical composition according to claim 2, further comprising a K39 Leishmania antigen.

5. A pharmaceutical composition comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a Leishmania antigen, wherein said antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NO:80, 81, and 83-87, the polypeptide being present in an amount effective for the treatment of Leishmaniasis.

6. A pharmaceutical composition according to claim 5 further comprising a K39 Leishmania antigen.

7. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO:61, wherein said polypeptide comprises an immunogenic portion of a Leishmania antigen, said immunogenic portion of Leishmania antigen selectively binds to

anti-leishmania antibodies.

8. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO:62, wherein said polypeptide comprises an immunogenic portion of a Leishmania antigen, said immunogenic portion of Leishmania antigen selectively binds to anti-leishmania antibodies.

9. An isolated polypeptide comprising SEQ ID NO:80.

10. An isolated polypeptide comprising SEQ ID NO:81.

11. An isolated polypeptide comprising SEQ ID NO:83.

12. An isolated polypeptide comprising SEQ ID NO:84.

13. An isolated polypeptide comprising SEQ ID NO:85.

14. An isolated polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 86 and 87.

Previous Doc Next Doc Go to Doc#

L15: Entry 43 of 71 File: USPT Dec 31, 2002

DOCUMENT-IDENTIFIER: US 6500437 B1

TITLE: Leishmania antigens for use in the therapy and diagnosis of leishmaniasis

Abstract Text (1):
Compositions and methods for preventing, treating and detecting leishmaniasis and stimulating immune responses in patients are disclosed. The compounds provided include polypeptides that contain at least an immunogenic portion of one or more Leishmania antigens, or a variant thereof. Vaccines and pharmaceutical compositions comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided and may be used, for example, for the prevention and therapy of leishmaniasis, as well as for the detection of Leishmania infection.

Brief Summary Text (2):
The present invention relates generally to compositions and methods for preventing, treating and detecting leishmaniasis, and for stimulating immune responses in patients. The invention is more particularly related to polypeptides comprising an immunogenic portion of a Leishmania antigen or a variant thereof, and to vaccines and pharmaceutical compositions comprising one or more such polypeptides. The vaccines and pharmaceutical compositions may be used, for example, for the prevention and therapy of leishmaniasis, as well as for the detection of Leishmania infection.

Brief Summary Text (4):
Leishmania organisms are intracellular protozoan parasites of macrophages that cause a wide range of clinical diseases in humans and domestic animals, primarily dogs. In some infections, the parasite may lie dormant for many years. In other cases, the host may develop one of a variety of forms of leishmaniasis. For example, the disease may be asymptomatic or may be manifested as subclinical visceral leishmaniasis, which is characterized by mild symptoms of malaise, diarrhea and intermittent hepatomegaly. Patients with subclinical or asymptomatic disease usually have low antibody titers, making Patients with subclinical or asymptomatic disease usually have low antibody titers, making the disease difficult to detect with standard techniques. Alternatively, leishmaniasis may be manifested as a cutaneous disease, which is a severe medical problem but is generally self-limiting, or as a highly destructive mucosal disease, which is not self-limiting. Finally, and most seriously, the disease may be manifested as an acute visceral infection involving the spleen, liver and lymph nodes, which, untreated, is generally a fatal disease. Symptoms of acute visceral leishmaniasis include hepatosplenomegaly, fever, leukopenia, anemia and hypergammaglobulinemia.

Brief Summary Text (6):
Accurate diagnosis of leishmaniasis is frequently difficult to achieve. There are 20 species of Leishmania that infect humans, including L. donovani, L. chagasi, L. infantum, L. major, L. amazonensis, L. braziliensis, L. panamensis, L. mexicana, L. tropica, and L. guyanensis, and there are no distinctive signs or symptoms that unambiguously indicate the presence of Leishmania infection. Parasite detection methods have been used, but such methods are neither sensitive nor clinically practical. Current skin tests typically use whole or lysed parasites. Such tests are generally insensitive, irreproducible and prone to cross-reaction with a variety of other diseases. In addition, the preparations employed in such tests are often unstable. Thus, there is a need for improved methods for the detection of Leishmania infection.

Brief Summary Text (9):

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Briefly stated, the present invention provides compositions and methods for preventing, treating and detecting leishmaniasis, as well as for stimulating immune responses in patients. In one aspect, polypeptides are provided which comprise at least an immunogenic portion of a Leishmania antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In specific embodiments of the invention, the Leishmania antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 4, 20, 22, 24, 26, 36-38, 41, 50-53 and 82. DNA sequences encoding the above polypeptides, recombinant expression vectors comprising these DNA sequences and host cells transformed or transfected with such expression vectors are also provided.

Brief Summary Text (10):
In further aspects, the present invention provides fusion proteins comprising Leishmania antigens, together with polynucleotides encoding such fusion proteins. In certain specific embodiments, such fusion proteins comprise an amino acid sequence selected from the group consisting of SEQ ID NO: 95, 96 and 97.

Brief Summary Text (11):
In related aspects, the present invention provides pharmaceutical compositions which comprise one or more of the polypeptides and/or fusion proteins described herein, or a polynucleotide encoding such polypeptides and fusion proteins, and a physiologically acceptable carrier. Vaccines which comprise one or more such polypeptides, fusion proteins or polynucleotides, together with an immunostimulant are also provided. In specific embodiments of these aspects, the Leishmania antigen has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 4, 20, 22, 24, 26, 36-38, 41, 50-53 and 82.

Brief Summary Text (12):
In still further related embodiments, the pharmaceutical compositions and vaccines comprise at least two different polypeptides, each polypeptide comprising an immunogenic portion of a Leishmania antigen having an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 2, 4, 6, 8, 10, 20, 22, 24, 26, 36-38, 41, 50-53, 82, and variants thereof that differ only in conservative substitutions and/or modifications. In other embodiments, the inventive pharmaceutical compositions comprise one or more of the inventive polypeptides in combination with a known Leishmania antigen.

Brief Summary Text (13):
In yet other related embodiments, the pharmaceutical compositions and vaccines comprise soluble Leishmania antigens.

Brief Summary Text (15):
In further aspects, methods and diagnostic kits are provided for detecting Leishmania infection in a patient. The methods comprise: (a) contacting dermal cells of a patient with a pharmaceutical composition as described above; and (b) detecting an immune response on the patient's skin, therefrom detecting Leishmania infection in the patient. The diagnostic kits comprise: (a) a pharmaceutical composition as described above; and (b) an apparatus sufficient to contact the pharmaceutical composition with the dermal cells of a patient.

Drawing Description Text (4):
FIG. 3 illustrates the expression and purification of the Leishmania antigen Ldp23 as a recombinant fusion protein. Panel A shows a Coomassie blue-stained SDS-PAGE gel of lysed E. coli without (lane 1) and with (lane 2) IPTG induction of Ldp23 expression. Arrow indicates the recombinant fusion protein. Panel B shows the fusion protein following excision from a preparative SDS-PAGE gel, electroelution, dialysis against PBS and analytical SDS-PAGE.

Drawing Description Text (8):
FIG. 7 shows the stimulation of Leishmania-specific T-cell proliferation by Ldp23. The results are presented as relative cell number as a function of fluorescence intensity. T-cells (10.sup.5 /well) were purified from lymph nodes of BALB/c mice immunized in the foot pad with L. donovani promastigotes in CFA and were cultured with various concentrations of the purified recombinant Ldp23 in the presence of

2.times.10.sup.5 Mitomycin C-treated normal BALB/c spleen mononuclear cells. Proliferation of T-cells was measured at 27 hours of culture. Values are expressed as cpm and represent the mean of [.sup.3 H]TdR incorporation of triplicate cultures.

Drawing Description Text (9):
FIG. 8 illustrates Ldp23-induced cytokine production by lymph node cells of BALB/c mice. Cultures were incubated with varying amounts of Ldp23 or Leishmania lysate, presented as .mu.g/mL, and were assayed by ELISA for the production of interferon-.gamma. (panel A) or interleukin-4 (panel B), both of which are shown as ng/mL.

Drawing Description Text (10):
FIG. 9 shows the PCR amplification of cytokine mRNAs isolated from mucosal leishmaniasis (Panel A) and cutaneous leishmaniasis (panel B) patient PBMC before and after stimulation with representative polypeptides of the present invention. Lanes O and--indicate the level of PCR products at the initiation of culture and after 72 hours of culture, respectively, in the absence of added polypeptide; lanes Lb, 83a and 83b indicate the level of PCR products following culturing of PBMC with L. braziliensis lysate, and the Leishmania antigens Lbhsp83a and Lbhsp83b, respectively.

Drawing Description Text (11):
FIG. 10 presents a comparison of the levels of interferon-.gamma. (panel A) and TNF-.alpha. (panel B) in the supernatants of 72 hour PBMC cultures from Leishmania-infected and control individuals in response to stimulation with parasite lysate or the indicated polypeptides.

Drawing Description Text (12):
FIG. 11 illustrates the levels of IL-10p40 (in pg/mL) in the supernatant of PBMC cultures from L. braziliensis-infected individuals and uninfected controls 72 hours following stimulation with parasite promastigote lysate (Lb), Lbhsp83a or Lbhsp83b.

Drawing Description Text (15):
FIG. 14 shows the level of IFN-.gamma. (in pg/mL) secreted by Leishmania-infected and uninfected human PBMC stimulated by the Leishmania antigen M15, as compared to the levels stimulated by L. major lysate and L-Rack, an antigen that does not appear to be recognized by Leishmania-infected humans.

Drawing Description Text (16):
FIG. 15 shows the level of IFN-.gamma. (in pg/mL) secreted by infected and uninfected human PBMC stimulated by soluble Leishmania antigens (S antigens), as compared to the levels stimulated by L. major lysate and L-Rack.

Drawing Description Text (18):
FIG. 17 shows the proliferation of human PBMC, prepared from Leishmania-immune and uninfected individuals, stimulated by M15 as compared to the proliferation stimulated by L. major lysate and L-Rack. Values are expressed as cpm.

Drawing Description Text (19):
FIG. 18 illustrates the proliferation of human PBMC, prepared from Leishmania-infected and uninfected individuals, stimulated by soluble Leishmania antigens as compared to the proliferation stimulated by culture medium, L. major lysate and L-Rack. Values are expressed as cpm.

Drawing Description Text (21):
FIG. 20 illustrates the reactivity of rabbit sera raised against soluble Leishmania antigens with Leishmania promastigote lysate (lane 1) and soluble Leishmania antigens (lane 2).

Drawing Description Text (22):
FIG. 21 shows the cDNA and predicted amino acid sequence for the Leishmania antigen Lmspla.

Drawing Description Text (23):
FIG. 22 shows a Southern blot of genomic DNA from L. major digested with a panel of restriction enzymes (lanes 1 to 7) and six other Leishmania species digested with PstI (lanes 8 to 13) probed with the full-length cDNA insert of Lmspla.

Drawing Description Text (24):
FIG. 23 shows a Southern blot of genomic DNA from L. major digested with a panel of restriction enzymes, six other Leishmania species digested with PstI and the infectious pathogens T. cruzi and T. brucei, probed with the full-length cDNA insert of the Leishmania antigen MAPS-1A.

Drawing Description Text (29):
FIG. 28 illustrates the effectiveness of immunization with either soluble Leishmania antigens or a mixture of Ldp23, LbeiF4A and M15 plus adjuvant in conferring protection against infection (as measured by footpad swelling) in a murine leishmaniasis model system, as compared to the administration of adjuvant alone.

Drawing Description Text (32):
FIG. 31 illustrates the effectiveness of immunization with soluble Leishmania antigens, MAPS-1A and M15 plus adjuvant, IL-12, in conferring protection against infection (as measured by footpad swelling) in a murine leishmaniasis model system, as compared to the administration of adjuvant IL-12 alone.

Drawing Description Text (34):
FIG. 33 illustrates the effectiveness of immunization with Leishmania fusion proteins plus IL-12 as adjuvant, in conferring protection against infection in a murine leishmaniasis model system.

Drawing Description Text (35):
FIG. 34 illustrates the effectiveness of immunization with Leishmania fusion proteins plus the adjuvant MPL-SE, in conferring protection against infection in a murine leishmaniasis model system.

Detailed Description Text (2):
As noted above, the present invention is generally directed to compositions and methods for preventing, treating and detecting leishmaniasis, as well as for stimulating immune responses in patients. The compositions of the subject invention include polypeptides that comprise at least an immunogenic portion of a Leishmania antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one preferred embodiment, compositions of the present invention include multiple polypeptides selected so as to provide enhanced protection against a variety of Leishmania species.

Detailed Description Text (3):
Polypeptides within the scope of the present invention include, but are not limited to, polypeptides comprising immunogenic portions of Leishmania antigens comprising the sequences recited in SEQ ID NO:2 (referred to herein as M15), SEQ ID NO:4 (referred to herein as Ldp23), SEQ ID NO:6 (referred to herein as Lbhsp83), SEQ ID NO:8 (referred to herein as Lt-210), SEQ ID NO:10 (referred to herein as LbeIF4A), SEQ ID NO: 20 (referred to herein as Lmspla), SEQ ID NO: 22 (referred to herein as Lmsp9a), SEQ ID NOs: 24 and 26 (referred to herein as MAPS-1A), and SEQ ID NO: 36-42, 49-53 and 55. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (i.e., antigens), wherein the amino acid residues are linked by covalent bonds. Thus, a polypeptide comprising an immunogenic portion of one of the above antigens may consist entirely of the immunogenic portion, or may contain additional sequences. The additional sequences may be derived from the native Leishmania antigen or may be heterologous, and such sequences may (but need not) be immunogenic. An antigen "having" a particular sequence is an antigen that contains, within its full length sequence, the recited sequence. The native antigen may, or may not, contain additional amino acid sequence.

Detailed Description Text (4):

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An immunogenic portion of a Leishmania antigen is a portion that is capable of eliciting an immune response (i.e., cellular and/or humoral) in a presently or previously Leishmania-infected patient (such as a human or a dog) and/or in cultures of lymph node cells or peripheral blood mononuclear cells (PBMC) isolated from presently or previously Leishmania-infected individuals. The cells in which a response is elicited may comprise a mixture of cell types or may contain isolated component cells (including, but not limited to, T-cells, NK cells, macrophages, monocytes and/or B cells). In particular, immunogenic portions are capable of inducing T-cell proliferation and/or a dominantly Th1-type cytokine response (e.g., IL-2, IFN-.gamma., and/or TNF-.alpha. production by T-cells and/or NK cells; and/or IL-12 production by monocytes, macrophages and/or B cells). Immunogenic portions of the antigens described herein may generally be identified using techniques known to those of ordinary skill in the art, including the representative methods provided herein.

Detailed Description Text (9):
"Polypeptides" as described herein also include combination polypeptides, also referred to as fusion proteins. A "combination polypeptide" is a polypeptide comprising at least one of the above immunogenic portions and one or more additional immunogenic Leishmania sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (ie., with no intervening amino acids) or may be joined by way of a linker sequence (e.g., Gly-Cys-Gly) that does not significantly diminish the immunogenic properties of the component polypeptides.

Detailed Description Text (12):
The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide. The preparation of fusion proteins of Leishmania antigens is described below in Example 19.

Detailed Description Text (13):
In general, Leishmania antigens having immunogenic properties, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures from one or more Leishmania species including, but not limited to, L. donovani, L. chagasi, L. infantum, L. major, L. amazonensis, L. braziliensis, L. panamensis, L. mexicana, L. tropica, and L. guyanensis. Such species are available, for example, from the American Type Culture Collection (ATCC), Rockville, Md. For example, peptides isolated from MHC class II molecules of macrophages infected with a Leishmania species may be used to rescue the corresponding Leishmania donor antigens. MHC class II molecules are expressed mainly by cells of the immune system, including macrophages. These molecules present peptides, which are usually 13-17 amino acids long, derived from foreign antigens that are degraded in cellular vesicles. The bound peptide antigens are then recognized by CD4 T-cells. Accordingly, foreign peptides isolated from MHC class II molecules of, for example, Leishmania-infected murine macrophages may be used to identify immunogenic Leishmania proteins.

Detailed Description Text (14):
Briefly, peptides derived from Leishmania antigens may be isolated by comparing the reverse phase HPLC profile of peptides extracted from infected macrophages with the profile of peptides extracted from uninfected cells. Peptides giving rise to distinct HPLC peaks unique to infected macrophages may then be sequenced using, for example, Edman chemistry as described in Edman and Berg, Eur J. Biochem, 80:116-132 (1967). A DNA fragment corresponding to a portion of a Leishmania gene encoding the peptide may then be amplified from a Leishmania cDNA library using an oligonucleotide sense primer derived from the peptide sequence and an oligo dT antisense primer. The resulting DNA fragment may then be used as a probe to screen a Leishmania library for a full length cDNA or genomic clone that encodes the Leishmania antigen. Such screens may generally be performed using techniques well known to those of ordinary skill in the art, such as those described in Sambrook et

al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y. (1989).

Detailed Description Text (15):
This approach may be used to identify a 23 kD Leishmania donovani antigen (referred to herein as Ldp23). The sequence of a polynucleotide encoding Ldp23 is provided in SEQ ID NO:3 and the amino acid sequence of Ldp23 is provided in SEQ ID NO:4. Using the methods described herein, Ldp23 has been shown to induce a Th1 immune response in T-cells prepared from Leishmania-infected mice.

Detailed Description Text (16):
Alternatively, a Leishmania cDNA or genomic expression library may be screened with serum from a Leishmania-infected individual, using techniques well known to those of ordinary skill in the art. Polynucleotides encoding reactive antigens may then be used to express the recombinant antigen for purification. The immunogenic properties of the purified Leishmania antigens may then be evaluated using, for example the representative methods described herein.

Detailed Description Text (17):
For example, sera from Leishmania-infected mice may be used to screen a cDNA library prepared from Leishmania amastigotes. Reactive clones may then be expressed and recombinant proteins assayed for the ability to stimulate T-cells or NK cells derived from Leishmania-immune individuals (i.e., individuals having evidence of infection, as documented by positive serological reactivity with Leishmania-specific antibodies and/or a Leishmania-specific DTH response, without clinical symptoms of leishmaniasis). This procedure may be used to obtain a recombinant polynucleotide encoding the Leishmania antigen designated M15. The sequence of such a polynucleotide is provided in SEQ ID NO:1, and the amino acid sequence of the encoded protein is provided in SEQ ID NO:2.

Detailed Description Text (18):
A similar approach may be used to isolate a genomic polynucleotide encoding an immunogenic Leishmania braziliensis antigen, referred to herein as Lbhsp83. More specifically, a genomic clone encoding Lbhsp83 may be isolated by screening a L. braziliensis expression library with sera from a Leishmania-infected individual. The DNA encoding Lbhsp83 is homologous to the gene encoding the eukaryotic 83 kD heat shock protein. The sequence of a polynucleotide encoding nearly all of Lbhsp83 is presented in SEQ ID NO:5, and the encoded amino acid sequence is provided in SEQ ID NO:6. Using the methods described below, Lbhsp83 has been found to stimulate proliferation, and a mixed Th1 and Th2 cytokine profile, in PBMC isolated from L. braziliensis-infected patients. Accordingly, Lbhsp83 is an immunogenic Leishmania antigen. Regions of Lbhsp83 that are not conserved with the mammalian gene have been found to be particularly potent for T-cell stimulation and antibody binding. Such regions may be identified, for example, by visual inspection of the sequence comparison provided in FIG. 19.

Detailed Description Text (20):
The above approach may further be used to isolate a polynucleotide encoding a L. braziliensis antigen referred to herein as LbeIF4A. Briefly, such a clone may be isolated by screening a L. braziliensis expression library with sera obtained from a patient afflicted with mucosal leishmaniasis, and analyzing the reactive antigens for the ability to stimulate proliferative responses and preferential Th1 cytokine production in PBMC isolated from Leishmania-infected patients, as described below. The preparation and characterization of LbeIF4A is described in detail in U.S. patent application Ser. Nos. 08/454,036 and 08/488,386, which are continuations-in-part of U.S. patent application Ser. No. 08/232,534, filed Apr. 22, 1994. The sequence of a polynucleotide encoding LbeIF4A is provided in SEQ ID NO:9 and the encoded amino acid sequence is presented in SEQ ID NO:10. Homologs of LbeIF4A, such as that found in L. major, may also be isolated using this approach, and are within the scope of the present invention.

Detailed Description Text (21):
Compositions of the present invention may also, or alternatively, contain soluble Leishmania antigens. As used herein, "soluble Leishmania antigens" refers to a

mixture of at least 8 different Leishmania antigens that may be isolated from the supernatant of Leishmania promastigotes of any species grown for 8-12 hours in protein-free medium. Briefly, the organisms are grown to late log phase in complex medium with serum until they reach a density of 2-3.times.10.sup.7 viable organisms per mL of medium. The organisms are thoroughly washed to remove medium components and resuspended at 2-3.times.10.sup.7 viable organisms per mL of defined serum-free medium consisting of equal parts RPMI 1640 and medium 199, both from Gibco BRL, Gaithersburg, Md. After 8-12 hours. the supernatant containing soluble Leishmania antigens is removed, concentrated 10 fold and dialyzed against phosphate-buffered saline for 24 hours. The presence of at least eight different antigens within the mixture of Leishmania antigens may be confirmed using SDS-PAGE (i.e., through the observation of at least 8 different bands). The immunogenic properties of the soluble Leishmania antigens may be confirmed by evaluating the ability of the preparation to elicit an immune response in cultures of lymph node cells and/or peripheral blood mononuclear cells (PBMC) isolated from presently or previously Leishmania-infected individuals. Such an evaluation may be performed as described below.

Detailed Description Text (22):
Individual antigens present within the mixture of soluble Leishmania antigens may be isolated by immunizing mice or rabbits with Leishmania culture supernatant, containing soluble antigens, and employing the resultant sera to screen a Leishmania cDNA expression library as described in detail below. This procedure may be used to isolate recombinant polynucleotides encoding the L. major antigens referred to herein as Lmsp1a, Lmsp9a and MAPS-1A. DNA sequences encoding Lmsp1a, Lmsp9a and MAPS-1A are provided in SEQ ID NO: 19, 21 and 23, respectively, with the corresponding predicted amino acid sequences being presented in SEQ ID NO: 20, 22 and 24, respectively. Similarly, sera from mice or rabbits immunized with L. major culture supernatant may be used to screen an L. major genomic DNA library. As detailed below, this procedure may be used to isolate polynucleotides encoding the L. major antigens referred to herein as LmgSP1, LmgSP3, LmgSP5, LmgSP8, LmgSP9, LmgSP13, LmgSP19, and polynucleotides encoding the L. chagasi antigens LcgSP1, LcgSP3, LcgSP4, LcgSP8, and LcgSP10. The DNA sequences encoding these antigens are provided in SEQ ID NO:29-35 and 44-48, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 36-42 and 49-53. The L. major antigens referred to herein as 1G6-34, 1E6-44, 4A5-63, 1B11-39, 2A10-37, 4G2-83, 4H6-41 and 8G3-100 may be isolated by means of CD4+ T cell expression cloning as described below. DNA sequences encoding these antigens are provided in SEQ ID NO: 72-79, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 80-87. The immunogenic properties of the isolated Leishmania antigens may be evaluated using, for example, the representative methods described herein.

Detailed Description Text (23):
Regardless of the method of preparation, the antigens described herein are immunogenic. In other words, the antigens (and immunogenic portions thereof) are capable of eliciting an immune response in cultures of lymph node cells and/or peripheral blood mononuclear cells (PBMC) isolated from presently or previously Leishmania-infected individuals. More specifically, the antigens, and immunogenic portions thereof, have the ability to induce T-cell proliferation and/or to elicit a dominantly Th1-type cytokine response (e.g., IL-2, IFN-.gamma., and/or TNF-.alpha. production by T-cells and/or NK cells; and/or IL-12 production by monocytes, macrophages and/or B cells) in cells isolated from presently or previously Leishmania-infected individuals. A Leishmania-infected individual may be afflicted with a form of leishmaniasis (such as subclinical, cutaneous, mucosal or active visceral) or may be asymptomatic. Such individuals may be identified using methods known to those of ordinary skill in the art. Individuals with leishmaniasis may be identified based on clinical findings associated with at least one of the following: isolation of parasite from lesions, a positive skin test with Leishmania lysate or a positive serological test. Asymptomatic individuals are infected individuals who have no signs or symptoms of the disease. Such individuals can be identified based on a positive serological test and/or skin test with Leishmania lysate.

Detailed Description Text (24):

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The term "PBMC," which refers to a preparation of nucleated cells consisting primarily of lymphocytes and monocytes that are present in peripheral blood, encompasses both mixtures of cells and preparations of one or more purified cell types. PBMC may be isolated by methods known to those in the art. For example, PBMC may be isolated by density centrifugation through, for example, Ficoll.TM. (Winthrop Laboratories, New York). Lymph node cultures may generally be prepared by immunizing BALB/c mice (e.g., in the rear foot pad) with Leishmania promastigotes emulsified in complete Freund's adjuvant. The draining lymph nodes may be excised following immunization and T-cells may be purified in an anti-mouse Ig column to remove the B cells, followed by a passage through a Sephadex G10 column to remove the macrophages. Similarly, lymph node cells may be isolated from a human following biopsy or surgical removal of a lymph node.

Detailed Description Text (25):
The ability of a polypeptide (e.g., a Leishmania antigen or a portion or other variant thereof) to induce a response in PBMC or lymph node cell cultures may be evaluated by contacting the cells with the polypeptide and measuring a suitable response. In general, the amount of polypeptide that is sufficient for the evaluation of about 2.times.10.sup.5 cells ranges from about 10 ng to about 100 .mu.g, and preferably is about 1-10 .mu.g. The incubation of polypeptide with cells is typically performed at 37.degree. C. for about 1-3 days. Following incubation with polypeptide, the cells are assayed for an appropriate response. If the response is a proliferative response, any of a variety of techniques well known to those of ordinary skill in the art may be employed. For example, the cells may be exposed to a pulse of radioactive thymidine and the incorporation of label into cellular DNA measured. In general, a polypeptide that results in at least a three fold increase in proliferation above background (i.e., the proliferation observed for cells cultured without polypeptide) is considered to be able to induce proliferation.

Detailed Description Text (26):
Alternatively, the response to be measured may be the secretion of one or more cytokines (such as interferon-.gamma. (IFN-.gamma.), interleukin-4 (IL-4), interleukin-12 (p70 and/or p40), interleukin-2 (IL-2) and/or tumor necrosis factor-.alpha. (TNF-.alpha.)) or the change in the level of mRNA encoding one or more specific cytokines. In particular, the secretion of interferon-.gamma., interleukin-2, tumor necrosis factor-.alpha. and/or interleukin-12 is indicative of a Th1 response, which is responsible for the protective effect against Leishmania. Assays for any of the above cytokines may generally be performed using methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA). Suitable antibodies for use in such assays may be obtained from a variety of sources such as Chemicon, Temucula, Calif. and PharMingen, San Diego, Calif., and may generally be used according to the manufacturer's instructions. The level of mRNA encoding one or more specific cytokines may be evaluated by, for example, amplification by polymerase chain reaction (PCR). In general, a polypeptide that is able to induce, in a preparation of about 1-3.times.10.sup.5 cells, the production of 30 pg/mL of IL-12, IL-4, IFN-.gamma., TNF-.alpha. or IL-12 p40, or 10 pg/mL of IL-12 p70, is considered able to stimulate production of a cytokine.

Detailed Description Text (28):
Portions and other variants of immunogenic Leishmania antigens may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystemsDivision, Foster City, Calif., and may be operated according to the manufacturer's instructions.

Detailed Description Text (31):

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In another aspect, the present invention provides epitope repeat sequences, or antigenic epitopes, of a Leishmania antigen, together with polypeptides comprising at least two such contiguous antigenic epitopes. As used herein an "epitope" is a portion of an antigen that reacts with sera from Leishmania-infected individuals (i.e. an epitope is specifically bound by one or more antibodies present in such sera). As discussed above, epitopes of the antigens described in the present application may be generally identified using techniques well known to those of skill in the art.

Detailed Description Text (32):
In one embodiment, antigenic epitopes of the present invention comprise an amino acid sequence provided in SEQ ID NO:43, 56, 57 or 58. As discussed in more detail below, antigenic epitopes provided herein may be employed in the diagnosis and treatment of Leishmania infection, either alone or in combination with other Leishmania antigens or antigenic epitopes. Antigenic epitopes and polypeptides comprising such epitopes may be prepared by synthetic means, as described generally above and in detail in Example 15.

Detailed Description Text (33):
In certain aspects of the present invention, described in detail below, the polypeptides, antigenic epitopes and/or soluble Leishmania antigens may be incorporated into pharmaceutical compositions or vaccines. For clarity, the term "polypeptide" will be used when describing specific embodiments of the inventive therapeutic compositions and diagnostic methods. However, it will be clear to one of skill in the art that the antigenic epitopes of the present invention may also be employed in such compositions and methods. Pharmaceutical compositions comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. Vaccines comprise one or more of the above polypeptides and an immunostimulant, such as an adjuvant (e.g., LbeIF4A, interleukin-12 or other cytokines) or a liposome (into which the polypeptide is incorporated). In certain embodiments, the inventive vaccines include an adjuvant capable of eliciting a predominantly Th-1 type response. Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, Mont.; see U.S. Pat. Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555 and WP 99/33488. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila, United States), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Detailed Description Text (34):
Vaccines may additionally contain a delivery vehicle, such as a biodegradable microsphere (disclosed, for example, in U.S. Pat. Nos. 4,897,268 and 5,075,109). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other Leishmania antigens, either incorporated into a combination polypeptide or present within one or more separate polypeptides.

Detailed Description Text (38):
In one preferred embodiment, compositions of the present invention include multiple polypeptides selected so as to provide enhanced protection against a variety of Leishmania species. Such polypeptides may be selected based on the species of origin of the native antigen or based on a high degree of conservation of amino acid sequence among different species of Leishmania. A combination of individual polypeptides may be particularly effective as a prophylactic and/or therapeutic

vaccine because (1) stimulation of proliferation and/or cytokine production by a combination of individual polypeptides may be additive, (2) stimulation of proliferation and/or cytokine production by a combination of individual polypeptides may be synergistic, (3) a combination of individual polypeptides may stimulate cytokine profiles in such a way as to be complementary to each other and/or (4) individual polypeptides may be complementary to one another when certain of them are expressed more abundantly on the individual species or strain of Leishmania responsible for infection. A preferred combination contains polypeptides that comprise immunogenic portions of M15, Ldp23, Lbhsp83, Lt-1 and LbeIF4A. Alternatively, or in addition, the combination may include one or more polypeptides comprising immunogenic portions of other Leishmania antigens disclosed herein, and/or soluble Leishmania antigens.

Detailed Description Text (39):
In another preferred embodiment, compositions of the present invention include single polypeptides selected so as to provide enhanced protection against a variety of Leishmania species. A single individual polypeptide may be particularly effective as a prophylactic and/or therapeutic vaccine for those reasons stated above for combinations of individual polypeptides.

Detailed Description Text (40):
In another embodiment, compositions of the present invention include individual polypeptides and combinations of the above described polypeptides employed with a variety of adjuvants, such as IL-12 (protein or DNA) to confer a protective response against a variety of Leishmania species.

Detailed Description Text (41):
In yet another embodiment, compositions of the present invention include DNA constructs of the various Leishmania species employed alone or in combination with variety of adjuvants, such as IL-12 (protein or DNA) to confer a protective response against a variety of Leishmania species.

Detailed Description Text (42):
The above pharmaceutical compositions and vaccines may be used, for example, to induce protective immunity against Leishmania in a patient, such as a human or a dog, to prevent leishmaniasis. Appropriate doses and methods of administration for this purposes are described in detail below.

Detailed Description Text (43):
The pharmaceutical compositions and vaccines described herein may also be used to stimulate an immune response, which may be cellular and/or humoral, in a patient. For Leishmania-infected patients, the immune responses that may be generated include a preferential Th1 immune response (i.e., a response characterized by the production of the cytokines interleukin-1, interleukin-2, interleukin-12 and/or interferon-.gamma., as well as tumor necrosis factor-.alpha.). For uninfected patients, the immune response may be the production of interleukin-12 and/or interleukin-2, or the stimulation of gamma delta T-cells. In either category of patient, the response stimulated may include IL-12 production. Such responses may also be elicited in biological samples of PBMC or components thereof derived from Leishmania-infected or uninfected individuals. As noted above, assays for any of the above cytokines may generally be performed using methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA).

Detailed Description Text (44):
Suitable pharmaceutical compositions and vaccines for use in this aspect of the present invention are those that contain at least one polypeptide comprising an immunogenic portion of a Leishmania antigen disclosed herein (or a variant thereof). Preferably, the polypeptides employed in the pharmaceutical compositions and vaccines are complementary, as described above. Soluble Leishmania antigens, with or without additional polypeptides, may also be employed.

Detailed Description Text (45):
The pharmaceutical compositions and vaccines described herein may also be used to treat a patient afflicted with a disease responsive to IL-12 stimulation. The

patient may be any warm-blooded animal, such as a human or a dog. Such diseases include infections (which may be, for example, bacterial, viral or protozoan) or diseases such as cancer. In one embodiment, the disease is leishmaniasis, and the patient may display clinical symptoms or may be asymptomatic. In general, the responsiveness of a particular disease to IL-12 stimulation may be determined by evaluating the effect of treatment with a pharmaceutical composition or vaccine of the present invention on clinical correlates of immunity. For example, if treatment results in a heightened Th1 response or the conversion of a Th2 to a Th1 profile, with accompanying clinical improvement in the treated patient, the disease is responsive to IL-12 stimulation. Polypeptide administration may be as described below, or may extend for a longer period of time, depending on the indication. Preferably, the polypeptides employed in the pharmaceutical compositions and vaccines are complementary, as described above. A particularly preferred combination contains polypeptides that comprise immunogenic portions of M15, Ldp23, Lbhsp83, Lt-1 and LbeIF4A, Lmsp1a, Lmsp9a, and MAPS-1A. Soluble Leishmania antigens, with or without additional polypeptides, may also be employed.

Detailed Description Text (47):
In another aspect, this invention provides methods for using one or more of the polypeptides described above to diagnose Leishmania infection in a patient using a skin test. As used herein, a "skin test" is any assay performed directly on a patient in which a delayed-type hypersensitivity (DTH) reaction (such as induration and accompanying redness) is measured following intradermal injection of one or more polypeptides as described above. Such injection may be achieved using any suitable device sufficient to contact the polypeptide or polypeptides with dermal cells of the patient, such as a tuberculin syringe or 1 mL syringe. Preferably, the reaction is measured at least 48 hours after injection, more preferably 72 hours after injection.

Detailed Description Text (48):
The DTH reaction is a cell-mediated immune response, which is greater in patients that have been exposed previously to a test antigen (i.e., an immunogenic portion of a polypeptide employed, or a variant thereof). The response may measured visually, using a ruler. In general, induration that is greater than about 0.5 cm in diameter, preferably greater than about 1.0 cm in diameter, is a positive response, indicative of Leishmania infection, which may or may not be manifested as an active disease.

Detailed Description Text (49):
The polypeptides of this invention are preferably formulated, for use in a skin test, as pharmaceutical compositions containing at least one polypeptide and a physiologically acceptable carrier, as described above. Such compositions typically contain one or more of the above polypeptides in an amount ranging from about 1 .mu.g to 100 .mu.g, preferably from about 10 .mu.g to 50 .mu.g in a volume of 0.1 mL. Preferably, the carrier employed in such pharmaceutical compositions is a saline solution with appropriate preservatives, such as phenol and/or Tween 80.TM..

Detailed Description Text (50):
The inventive polypeptides may also be employed in combination with one or more known Leishmania antigens in the diagnosis of leishmaniasis, using, for example, the skin test described above. Preferably, individual polypeptides are chosen in such a way as to be complementary to each other. Examples of known Leishmania antigens which may be usefully employed in conjunction with the inventive polypeptides include K39 (Bums et al., Proc. Natl. Acad. Sci. USA, 1993 90:775-779).

Detailed Description Text (55):
This Example illustrates the preparation of a Leishmania antigen M15, having the sequence provided in SEQ ID NO:2.

Detailed Description Text (58):
The complete insert of clone pf1-1 was excised by digestion with BamHI/KpnI and was subcloned in frame into BamHI/KpnI digested pQE31 (QUIAGEN) to generate the

construct pM151A. E. coli containing this construct inducibly expressed high levels of the L. major antigen encoded by pfl1-1 (designated as M15) with the addition of a 6-histidine tag at the amino terminus. Large volume cultures (500 ml) of E. coil host cells containing the pM151A construct were induced to express recombinant protein by the addition of 2 mM IPTG at mid-log phase of growth. Growth was continued for 4 to 5 hours and bacteria were then pelleted and washed once with cold PBS. Bacteria ere resuspended in 20 ml of lysis buffer (50 mM Na.sub.2 HPO.sub.4, pH 8.0, 300 mM NaCl, 10 mM .beta.-mercaptoethanol) containing 20 mg of lysozyme and were lysed by a 1 hour incubation at 4.degree. C. followed by brief sonication. Insoluble material was removed by centrifugation at 10,000.times.g for 10 minutes and although the recombinant protein was found to be evenly distributed between the soluble and insoluble fractions the insoluble material was discarded at this point. Recombinant protein containing the amino terminal histidine tag was affinity purified using Ni-NTA resin (QIAGEN) according to the manufacturer's recommendations. Briefly, 8 ml of Ni-NTA resin resuspended in lysis buffer was added to the soluble lysate fraction and binding was conducted with constant mixing for 1 hour at 4.degree. C. The mixture was then loaded into a gravity flow column and the non-binding material was allowed to flow through. The Ni-NTA matrix was washed 3 times with 25 ml of wash buffer (50 mM Na.sub.2 HPO.sub.4, pH 6.0, 300 mM NaCl, 10 mM .beta.-mercaptoethanol) and bound material was eluted in 25 ml of elution buffer (50 mM Na.sub.2 HPO.sub.4, pH 5.0, 300 mM NaCl, 10 mM .beta.-mercaptoethanol). The eluted material was then dialyzed against 3 changes of PBS, sterile filtered and stored at -20.degree. C. The purified recombinant protein was shown by SDS-PAGE analysis to be free of any significant amount of E. coli protein. A small number of bands of lower molecular weight were assumed to be proteolytic products of the L. major antigen based on their reactivity by western blot analysis. A high titre polyclonal antisera against M15 was generated in rabbits by repeated subcutaneous injection of recombinant protein. Western blot analysis of lysates from L. major promastigotes and amastigotes using this antisera indicated that the protein is constitutively expressed throughout the parasite lifecycle.

Detailed Description Text (61):
This Example illustrates the preparation of a Leishmania antigen Ldp23, having the sequence provided in SEQ ID NO:4.

Detailed Description Text (63):
To ascertain that in vitro infection of macrophages would load their MHC class II molecules with parasite peptides, initial experiments were carried out to test the ability of L. donovani-infected macrophage cell line P388D1 to present parasite antigens to L. donovani specific T-cells. This macrophage cell line was chosen because it has the same H-2 haplotype as the BALB/c mouse, which is a strain of mouse moderately susceptible to L. donovani infection and selected to conduct the in vivo experiments. Using a proportion of 3-5 parasites per cell and an initial incubation at room temperature for 4-6 hours follows by 37.degree. C. for 24-48 hours, close to 90% of the macrophages were infected. The level of MHC class II molecule expression, as determined by FACS analysis, indicated that infection did not cause an effect on the levels of MHC class II expression when compared to non-infected control cells.

Detailed Description Text (64):
To test the ability of the L. donovani-infected P388D1 cells to present parasite antigens, macrophages were infected as indicated above and incubated at 26.degree. C. for 6 hours, and then as 37.degree. C. for either 24, 48 or 72 hours. At each of these time points the non-adherent cells and free parasites were washed out and the adherent cells were mechanically dislodged, washed and fixed with paraformaldehyde. These cells were then used as antigen presenting cells (APCs) for purified lymph node T-cells from BALB/c mice immunized with L. donovani promastigotes. To generate these anti-L. donovani specific T-cells, BALB/c mice (H-2.sup.d) of both sexes (The Jackson Laboratory, Bar Harbor, Me.) were immunized at 8 to 14 weeks of age in the rear foot pad with 5-10.times.10.sup.6 L. donovani promastigotes emulsified in complete Freund's adjuvant (CFA) (Difco Laboratories, Madison, Mich.) as described in Rodrigues et al., Parasite Immunol. 14:49 (1992). The draining lymph nodes were excised 8 days after the immunization and T-cells were purified in an anti-mouse Ig column to remove the B cells, as described in Bunn-Moreno and Campos-Neto, J.

Immunol. 127:427 (1981), followed by a passage through a Sephadex G10 column to remove the macrophages.

Detailed Description Text (69):
Out of three independent peptide extractions, twenty five distinct HPLC peptide peaks were isolated from L. donovani-infected macrophages and were subjected to protein sequence analysis using automated Edman degradation on an Applied Biosystems 477 gas-phase protein sequencer. Protein sequence and amino acid analysis were performed by the W.M. Keck Foundation, Biotechnology Resource Laboratory, Yale University. New Haven, Conn. In practically all determinations, no assignment could be made for the first position. Also, in most cases the definition of the amino acid residues of the 10-15 positions was based on the quantitative dominance of one residue over others. Using this approach, the sequences obtained for several peptides showed the presence of 3-6 different residues in many of the 10-15 sequence cycles analyzed for each determination, reflecting a mixture of peptides. In addition, sequences could not be obtained for some peaks because the peptides were blocked. Notwithstanding, three peptides sequences were determined. Amino-acid sequences were searched for identity with proteins in the GenBank database using the GENPETP, PIR and SWISSPROT programs. The sequence data base analysis revealed that one of the peptides was highly homologous to glyceraldehyde-3-phosphate dehydrogenase of various species. Another peptide had homology with elongation factor of several species, including Leishmania. The third sequence was not clearly related to any known proteins, and is shown below: XQXPQ(L/K)VFDEXX (SEQ ID NO:11).

Detailed Description Text (72):
The gene fragment was amplified from a L. donovani promastigote cDNA preparation using the following reaction conditions: one cycle of 3 min at 94.degree. C. immediately followed by 35 cycles of 1 min at 94.degree. C., 1 min at 45.degree. C. and 1 min at 72.degree. C. The L. donovani cDNA was prepared from 5.times.10.sup.7 washed promastigote forms harvested at the log growth phase (3 days culture). The cDNA was obtained using an Invitrogen cDNA cycle.TM. kit (Invitrogen Co., San Diego, Calif.). Oligonucleotide primers were synthesized by the DNA Synthesis Laboratory, Department of Pathology, Yale University School of Medicine.

Detailed Description Text (74):
The PCR amplified gene fragment was ligated into the pCR.TM. vector using the TA cloning system (Invitrogen Co., San Diego, Calif.). Transformants were selected in LB medium containing 100 .mu.g/ml ampicillin and the plasmid DNA was isolated using the Wizard.TM. Minipreps DNA purification kit (Promega Co., Madison, Wis.). Insert DNA was released with the restriction enzymes EcoRI and XhoI (New England Biolabs, Beverly, Mass.), purified from an agarose gel electrophoresis and labeled with .sup.32 P using a random priming method (Megaprime Labeling Kit, Amersham Life Science, Buckinghamshire, England).

Detailed Description Text (75):
This DNA fragment was used as probe to screen a L. donovani promastigote cDNA library as described in Skeiky et al., Infect. Immun. 62:1643 (1994). An approximately 650 bp cDNA (Ldp23) was excised from the phagemid by in vivo excision using the Stratagene protocol. DNA sequencing was performed using the Sequenase version 2 system (DNA sequencing kit) in the presence or absence of 7-deaza-GTP (United States Biochemical, Cleveland, Ohio). The sequence is provided as SEQ ID NO:3, and shows complete homology with the original 300 bp PCR fragment. A 525 bp open reading frame containing an ATG codon that follows the last 4 bases of the spliced leader sequence and 3 stop codons adjacent to the poly A tail was identified. This frame also codes the carboxyl terminal sequence (KVFDE) (SEQ ID NO:13) of the purified MHC class II associated peptide. The sequence analysis of the deduced protein sequence revealed one potential glycosylation site (Asn-Cys-Ser) at positions 68-70.

Detailed Description Text (82):
To ascertain that the Ldp23 peptide is expressed in Leishmania organisms, a Northern blot analysis was performed using RNA prepared from different promastigote growth phases (logarithmic and stationary) and from the amastigote form of these

parasites.

Detailed Description Text (83):
The RNA was prepared from 2.times.10.sup.7 parasite cells using the Micro RNA isolation kit (Stratagene, La Jolla, Calif.) according to the company's recommended instructions. RNA was prepared from L. donovani promastigotes (logarithmic growth phase); from L. major promastigotes (logarithmic and stationary growth phases); from L. amazonensis, both promastigotes (logarithmic and stationary growth phases) and amastigotes purified from CBA/J infected mice; and from L. pifanoi, both promastigotes (logarithmic and stationary growth phases) and amastigotes (from axenic culture medium). L. donovani (1S strain), L. amazonensis (MHOM/BR/77/LTB0016), L. major (MHOM/IR/79/LRC-L251) and L. pifanoi (MHOM/VE/60/Ltrod) promastigotes were grown and maintained at 26.degree. C. in Schneider's medium containing 20% FCS and 50 .mu.g/ml gentamicin. The amastigote forms of L. amazonensis were obtained by differential centrifugation of a "pus-like" foot pad lesion of a CBA/J mouse infected for 6 months with this parasite. L. pifanoi amastigotes were obtained from axenic culture as previously reported by Pan et al., J. Euk. Microbiol. 40:213 (1993).

Detailed Description Text (85):
FIG. 4 shows that one single RNA band of 680 bp was observed for all growth phases and forms of all tested Leishmania. Within FIG. 4, the numbers 1, 2 and 3 refer to RNA obtained from promastigotes at the logarithmic growth phase, promastigotes at the stationary growth phase and amastigote forms, respectively, and the numbers on the left side indicate the molecular weights of the markers in base pairs. This result is consistent with the corresponding gene size (525 bp) and with the molecular weight of the expressed protein and points to the ubiquitous distribution and expression of this gene within the genus Leishmania.

Detailed Description Text (88):
Sera were prepared and the anti-Leishmania antibody response was measured by Western blot analysis and by FACScan. In both cases L. donovani promastigotes were used as antigen. Approximately 2.times.10.sup.6 L. donovani promastigotes were grown in Schneider's medium for 3 days (log phase), were washed with PBS, lysed with SDS-PAGE loading buffer and submitted to electrophoresis under reducing conditions using a 15% polyacrylamide gel. The proteins were transferred onto 0.45.mu. Immobilon-P transfer membrane (Millipore Co., Bedford, Mass.) using a wet-type electroblotter (Mini Trans-Blot Electrophoretic Transfer Cell, Bio Rad Life Science Division, Richmond, Calif.) for 2 hours at 50 V. The membranes were blocked overnight at room temperature with PBS containing 3% normal goat serum (NGS), 0.2% Tween-20 and 0.05% sodium azide, followed by 3 washes with PBS. The blots were then incubated for 3-4 hours at 4.degree. C. with a 1/200 dilution of pre-immune rabbit serum (lane A, FIG. 5) or with the same dilution of anti-fusion protein rabbit antiserum (lane B, FIG. 5). The sera was previously absorbed 2.times. with non-viable desiccated Mycobacterium tuberculosis H-37 RA (Difco Laboratories, Detroit, Mich.) and were diluted in PBS containing 1% NGS and 5% powdered non-fat bovine milk (Carnation, Nestle Food Company, Glendale, Calif.). The membranes were then washed with PBS, incubated for 1 hour at room temperature with goat anti-rabbit IgG antibody conjugated with alkaline phosphatase (Promega, Madison, Wis.), washed once with PBS and 2.times. with veronal buffer pH 9.4. The reaction was visualized using the substrate mixture 5-bromo-4-chloro-3-indoyl-phosphate and nitroblue tetrazolium (Kirkegaard & Perry Laboratories Inc., Gaithersburg, Md.) according to the manufacturer's instructions.

Detailed Description Text (89):
FIG. 5 shows that the rabbit anti-recombinant protein antiserum detects a single protein of 23 kDa (Ldp23) in the Leishmania crude extract antigen preparation. No bands were observed when an anti-GST antiserum was used (not shown). Moreover, the FACScan analysis (FIG. 6) shows that the antibody induced by the recombinant Ldp23 reacts with intact live L. donovani promastigotes, thus pointing to a cell surface expression of this molecule on these organisms. The dotted line in FIG. 6 shows the indirect immunofluorescence performed using pre-immune mouse serum and the solid line in FIG. 6 shows the result obtained with mouse anti-GST-Ldp23 antiserun. Both sera were diluted at 1/100. Parasites were washed with staining buffer and

incubated with FITC conjugated goat anti-mouse immunoglobulin antibody. Fluorescence intensity was analyzed by FACScan.

Detailed Description Text (90):
F. Recognition of Recombinant Ldp23 by Leishmania-Specific Lymph Node T-cells

Detailed Description Text (91):
To test the responsiveness of T-cells to the Ldp23 protein, two sets of experiments were performed. In the first experiment, lymph node T-cells (10.sup.5 /well) from BALB/c mice immunized with L. donovani promastigotes (as described above) were stimulated to proliferate with 2.times.10.sup.5 Mitomycin C-treated normal mononuclear spleen cells (APC) and pulsed with the purified recombinant fusion protein. Proliferation of T-cells was measured at 72 hours of culture. Values are expressed in FIG. 7 as cpm and represent the mean of [.sup.3 H]TdR incorporation of triplicate cultures. Background cpm of cells (T cells+APC) cultured in the presence of medium alone was 1291. FIG. 7 shows that Leishmania specific T-cells proliferate well and in a dose response manner to recombinant Ldp23. No response was observed when purified GST was added instead of the recombinant fusion protein nor when lymph node T-cells from mice immunized with CFA alone were stimulated to proliferate in the presence of the Leishmanial fusion protein (not shown).

Detailed Description Text (92):
The recognition of the recombinant Ldp23 protein by Leishmania-specific T-cells was also tested using two murine models of leishmaniasis, the L. major highly susceptible BALB/c mice and the L. amazonensis susceptible CBA/J mice as described in Champsi and McMahon-Pratt, Infect. Immun. 56:3272 (1988). These models were selected to investigate the cytokine pattern induced by Ldp23. In the mouse model of leishmaniasis, resistance is associated with Th 1 cytokines while susceptibility is linked to Th 2 responses.

Detailed Description Text (93):
Lymph node cells were obtained 3 weeks after the initiation of infection of BALB/c mice with L. major and the ability of these cells to recognize the recombinant Ldp23 was measured by proliferation and by the production of the cytokines IFN-.gamma. and IL-4. 2.times.10.sup.6 cells obtained from the draining popliteal lymph node of infected mice were cultured for 72 hours in the presence of recombinant Ldp23 or Leishmania lysate. The levels of IFN-.gamma. and IL-4 in culture supernatants were measured by ELISA as previously described (Chatelain et al., J. Immunol. 148:1172 (1992), Curry et al., J. Immunol. Meth. 104:137 (1987), and Mossman and Fong, J. Immunol. Meth. 116:151 (1989)) using specific anti IFN-.gamma. and IL-4 monoclonal antibodies (PharMingen, San Diego, Calif.).

Detailed Description Text (94):
Ldp23 did stimulate these cells to proliferate (not shown) and induced a typical Th 1 type of cytokine response as indicated by the production of high levels of IFN-.gamma. (panel A of FIG. 8) and no IL-4 (panel B of FIG. 8). Stimulation of these cells with a Leishmania crude lysate yielded a mixed Th cytokine profile. Exactly the same pattern of cytokine production was obtained from the CBA/J mice infected with L. amazonensis (not shown). These results clearly indicate that Ldp23 is a powerful and selective activator of the Th 1 cytokines by mouse cells.

Detailed Description Text (97):
This Example illustrates the preparation of a Leishmania antigen Hsp83, having the sequence provided in SEQ ID NO:6.

Detailed Description Text (99):
Recombinant antigens produced by these clones were purified from 500 ml of isopropyl-.beta.-D-thiogalactopyranoside (IPTG)-induced cultures as described in Skeiky et al., J. Exp. Med. 176:201-211 (1992). These antigens were then assayed for the ability to stimulate PBMC from Leishmania-infected individuals to proliferate and secrete cytokine. Peripheral blood was obtained from individuals living in an area (Corte de Pedra, Bahia, Brazil) where L. braziliensis is endemic and where epidemiological, clinical, and immunological studies have been performed for over a decade, and PBMC were isolated from whole blood by density

centrifugation through Ficoll (Winthrop Laboratories, New York, N.Y.). For in vitro proliferation assays, 2.times.10.sup.5 to 4.times.10.sup.5 cells per well were cultured in complete medium (RPMI 1640 supplemented with gentamicin, 2-mercaptoethanol, L-glutamine, and 10% screened pooled A+ human serum; Trimar, Hollywood, Calif.) in 96-well flat-bottom plates with or without 10 .mu.g of the indicated antigens per ml or 5 .mu.g of phytohemagglutinin per ml (Sigma Immunochemicals, St. Louis, Mo.) for 5 days. The cells were then pulsed with 1 .mu.Ci of [.sup.3 H]thymidine for the final 18 h of culture. For determination of cytokine production 0.5 to 1 ml of PBMC was cultured at 1.times.10.sup.6 to 2.times.10.sup.6 cells per ml with or without the Leishmania antigens for 48 and 72 h.

Detailed Description Text (101):
A recombinant clone was identified in the above assays which, following sequence comparison of its predicted amino acid sequence with sequences of other proteins, was identified as a Leishmania braziliensis homolog of the eukaryotic 83 kD heat shock protein (Lbhsp83). The sequence of the clone is provided in SEQ ID NO:5 and the deduced protein sequence is provided in SEQ ID NO:6. On the basis of the homology, this clone, designated Lbhsp83a, appears to lack the first 47 residues of the full length 703 amino acid residues. Lbhsp83 has an overall homology of 94% (91% identity and 3% conservative substitution), 91% (84% identity and 7% conservative substitution) and 77% (61% identity and 16% conservative substitution) with L. amazonensis hsp83, T. cruzi hsp83 and human hsp89, respectively. A second clone (designated Lbhsp83b), which contained the 43 kD C-terminal portion of hsp83 (residues 331 to 703) was also isolated. FIG. 19 presents a comparison of the Lbhsp83 sequence with L. amazonensis hsp83(Lahsp83), T. cruzi hsp83 (Tchsp83) and human hsp89 (Huhsp89).

Detailed Description Text (102):
The results of proliferation assays using Lbhsp83a are shown in Table 1. Cells from all mucosal leishmaniasis (ML) patients proliferated strongly in response to Lbhsp83a, with stimulation indices (SIs) ranging from 19 to 558 (as compared to 20 to 1,634 for parasite lysate). Proliferation of PBMC from cutaneous leishmaniasis (CL) patients was variable and except for levels in two patients (IV and VII), levels were significantly lower than those of ML patients. By comparison, the proliferative responses of individuals with self-healing CL to Lbhsp83a were similar to those of individuals with ML. However, the responses of all six self-healing individuals to Lbhsp83 were consistently higher than those to Lbhsp83b. This suggests that PBMC from self-healing CL patients preferentially recognize one or more T-cell epitopes located within the amino portion of Lbhsp83.

Detailed Description Text (104):
In PBMC of three ML patients, stimulation with lysate resulted in increased expression of mRNA for IFN-.gamma., IL-2, and IL-4 but not IL-10. By comparison, both Lbhsp83 polypeptides elicited the production of mRNA for IFN-.gamma.and IL-2 from all ML patient PBMC tested. In contrast, profiles of mRNA for IL-10 and IL-4 differed for the two hsp83 polypeptides. Lbhsp83a stimulated the production of IL-10 but not IL-4 mRNA (patients I, II, III, and IV), while Lbhsp83b stimulated the production of IL-4 but not IL-10 mRNA in all six patients.

Detailed Description Text (105):
All CL patients tested responded to both Lbhsp83 polypeptides as well as to the parasite lysate by upregulating the synthesis of mRNAs for IL-2 and IFN-.gamma., and in two of four patients (I and IV), the level of IL-4 mRNA also increased, indicating stimulation of both Th1 and Th2 cytokines. Interestingly and as in the case of ML patient uncultured PBMC which did not have detectable levels of IL-10 mRNA, Lbhsp83a and not Lbhsp83b stimulated PBMC from one CL patient (IV) to synthesize IL-10 mRNA. However, in the other three patients (I, II, and III) with resting levels of IL-10 mRNA, both rLbhsp83 polypeptides as well as the parasite lysate downregulated the expression of IL-10 mRNA.

Detailed Description Text (106):
PBMC supernatants were also assayed for the presence of secreted IFN-.gamma., TNF-.alpha., IL-4, and IL-10. Cells from all ML and self-healing CL patients (seven and

six patients, respectively) and from four of seven CL patients were analyzed for secreted IFN-.gamma. following stimulation with both rLbhsp83 polypeptides, parasite lysate and Lbhsp70, an L. braziliensis protein homologous to the eukaryotic 70 kD heat shock protein (FIG. 10A). In general, rLbhsp83a stimulated patient PBMC to secrete higher levels of IFN-.gamma. than did rLbhsp83b (0.2 to 36 and 0.13 to 28 ng/ml, respectively). The presence of secreted IFN-.gamma. correlated well with the corresponding mRNA detected by PCR.

Detailed Description Text (107):
PBMC from four of five ML patients (I, II, V, and VII) had supernatant TNF-.alpha. levels (0.8 to 2.2 ng/ml) higher than those detected in cultures of PBMC from uninfected controls following stimulation with parasite lysate (FIG. 10B). Similarly, the same PBMC were stimulated by rLbhsp83 to produce levels of TNF-.alpha. in supernatant ranging from 0.61 to 2.9 ng/ml. Compared with those of uninfected controls, PBMC from three (I, V, and VI), five (I, II, IV, V, and VI), and two (II and V) of six individuals analyzed produced higher levels of TNF-.alpha. in response to parasite lysate, rLbhsp83a, and rLbhsp83b, respectively. The levels of TNF-.alpha. produced by PBMC from CL patients in response to parasite lysate were comparable to those produced by uninfected controls. However, rLbhsp83 stimulated TNF-.alpha. production in the PBMC of two of these patients. rLbhsp83a stimulated higher levels of TNF-.alpha. production than did rLbhsp83b. In the absence of antigen stimulation, only PBMC from ML patients (five of six) produced detectable levels of supernatant TNF-.alpha. (60 to 190 pg/ml).

Detailed Description Text (108):
In agreement with the IL-10 mRNA, IL-10 was detected by ELISA in the antigen-stimulated PMBC culture supernatants from ML and CL patients. The levels (49 to 190 pg) were significantly higher (up to 10-fold) following stimulation with rLbhsp83a compared with those after parallel stimulation of the same cells with rLbhsp83b (FIG. 11). Parasite lysate also stimulated PMBC from some of the patients to produce IL-10. Although rLbhsp83 stimulated PMBC from uninfected individuals to produce IL-10, with one exception, the levels were lower than those observed with patient PMBC. IL-4 was not detected in any of the supernatants analyzed. Therefore, the level of any secreted IL-4 is below the detection limit of the ELISA employed (50 pg/ml). Taken together, the results demonstrate that a predominant Th1-type cytokine profile is associated with PMBC from L. braziliensis-infected individuals following stimulation with rLbhsp83 polypeptides.

Detailed Description Text (109):
To determine the correlation between the observed T-cell responses and antibody production to Lbhsp83, we compared the antibody (immunoglobulin G) reactivities to Lbhsp83 in sera from the three patient groups (FIG. 12). The ELISA reactivities of ML patient sera with rLbhsp83a were comparable to those observed with parasite lysate, and in general, there was a direct correlation between ML patient anti-Lbhsp83 antibody titer and T-cell proliferation. Of 23 serum samples from ML patients analyzed, 22 were positive (.about.96%) with absorbance values of 0.20 to >3.0. Eleven of the ML patient serum samples had optical density values that were >1. In general, CL patients had significantly lower anti-Lbhsp83 antibody titers ({character pullout}=0.74; standard error of the mean [SEM]=0.1) compared to those of ML patients. Therefore, ML and CL patient anti-rhsp83 antibody titers correlated with their respective T-cell proliferative responses. Anti-rLbhsp83 antibody titers were significantly higher in patients with ML ({character pullout}=1.5; SEM=0.2) than in self-healing CL patients ({character pullout}=0.35; SEM=0.056), although their T-cell proliferative responses were similar. In fact, anti-Lbhsp83 antibody titers in serum from self-healing CL patients were comparable to those from uninfected controls ({character pullout}=0.24; SEM=0.028). By using 2 standard deviations greater than the mean absorbance value of uninfected control (0.484) as a criterion for positive reactivity to Lbhsp83, eight of nine of the self-healing patient serum samples tested were negative.

Detailed Description Text (112):
This Example illustrates the preparation of clones encoding portions of the Leishmania antigen Lt-210, and which has the sequence provided in SEQ ID NO:8.

Detailed Description Text (119):
Hybridization analysis confirmed that rLt-2 and rLt-1 contain overlapping sequences. Genomic DNAs of various Leishmania species were restricted with a variety of enzymes, separated by agarose gel electrophoresis, and blotted on Nytran membrane filter (Schleicher & Schuell, Keene, N.H.). Inserts from rLt-1 and rLt-2 were labeled with .sup.32 P-CTP by reverse transcriptase from random oligonucleotide primers and used as probes after separation from unincorporated nucleotides on a Sephadex G-50 column. Hybridizations using the rLt-1 or the rLt-2 probe are performed in 0.2M NaH.sub.2 PO.sub.4 /3.6 M NaCl at 65.degree. C., whereas hybridization using the rLt-1r probe is performed in 0.2 M NaH.sub.2 PO.sub.4 /3.6 M NaCl/0.2 M EDTA at 60.degree. C. overnight. Filters are washed in 0.075 M NaCl/0.0075 M sodium citrate pH 7.0 (0.15 M NaCl/0.0150 M sodium citrate for the Lt-1r probe), plus 0.5% SDS at the same temperature as hybridization.

Detailed Description Text (120):
Genomic DNA from a number of Leishmania species including L. tropica were analyzed by Southern blots as described above using the Lt-1, Lt-2, and Lt-1r inserts separately as probes. Collectively, various digests of L. tropica DNA indicate that this gene has a low copy nunber. A similar, overlapping pattern was observed using either the Lt-1 or Lt-2 insert as a probe, consistent with the premise that these two clones contain sequences near or overlapping one another. In addition, sequences hybridizing with these clones are present in other Leishmania species.

Detailed Description Text (128):
A recombinant clone was identified in the above assays which, following sequence comparison of its predicted amino acid sequence with sequences of other proteins, was identified as a Leishmania braziliensis homolog of the eukaryotic initiation factor 4A (eIF4A). The isolated clone (pLeIF.1) lacked the first 48 amino acid residues (144 nucleotides) of the full length protein sequence. The pLeIF.1 insert was subsequently used to isolate the full length genomic sequence.

Detailed Description Text (132):
This Example illustrates the preparation of soluble Leishmania antigens from an L. major culture supernatant. L. major promastigotes were grown to late log phase in complex medium with serum until they reached a density of 2-3.times.10.sup.7 viable organisms per mL of medium. The organisms were thoroughly washed to remove medium components and resuspended at 2-3.times.10.sup.7 viable organisms per mL of defined serum-free medium consisting of equal parts RPMI 1640 and medium 199, both from Gibco BRL, Gaithersburg, Md. After 8-12 hours, the supernatant was removed, concentrated 10 fold and dialyzed against phosphate-buffered saline for 24 hours. Protein concentration was then determined and the presence of at least eight different antigens confirmed by SDS-PAGE. This mixture is referred to herein as "soluble Leishmania antigens."

Detailed Description Text (134):
Comparison of Interleukin-4 and Interferon-.gamma. Production Stimulated by Leishmania Antigens

Detailed Description Text (135):
This Example illustrates the immunogenic properties of the antigens prepared according to Examples 1, 2, 5 and 6, as determined by their ability to stimulate IL-4 and IFN-.gamma. in lymph node cultures from infected mice and in human PBMC preparations. Lymph node cultures for use in these studies were prepared from L. major-infected BALB/c mice 10 days after infection, as described in Example 2. PBMC were prepared using peripheral blood obtained from individuals with cured L. donovani infections who were immunologically responsive to Leishmania. Diagnosis of the patients was made by clinical findings associated with at least one of the following: isolation of parasite from lesions, a positive skin test with Leishmania lysate or a positive serological test. Uninfected individuals were identified based on a lack of clinical signs or symptoms, a lack of history of exposure or travel to endemic areas, and the absence of a serological or cellular response to Leishmania antigens. Peripheral blood was collected and PBMC isolated by density centrifugation through FiColl.TM. (Winthrop Laboratories, New York).

Detailed Description Text (137):
FIGS. 13A and 13B, illustrate the mean level of secreted IL-4 and IFN-.gamma., respectively, 72 hours after addition of 10 .mu.g/mL of each of the following antigens to a lymph node culture prepared as described above: soluble Leishmania antigen (i.e., an extract prepared from ruptured promastigotes which contains membrane and internal antigens (SLA)), Ldp23, LbeIF4A (LeIF), Lbhsp83, M15 and LmeIF (the L. major homolog of LbeIF4A). The levels of secreted IL-4 and IFN-.gamma. in medium alone (i.e., unstimulated) are also shown. While SLA elicits a predominantly Th2 response from lymph node cells of Leishmania-infected mice, Ldp23, LbeIF4A, Lbhsp83 and M15 elicited relatively little IL-4 and large amounts of IFN-.gamma., consistent with a Th1 response profile.

Detailed Description Text (138):
FIG. 14 shows the level of secreted IFN-.gamma. in culture filtrate from infected and uninfected human PBMC preparations 72 hours after addition of 10 .mu.g/mL L. major lysate, M15 or L-Rack, an immunodominant leishmanial antigen in murine leishmaniasis. Similarly, FIG. 15 illustrates the level of secreted IFN-.gamma. in culture filtrate from infected and uninfected human PBMC preparations 72 hours after addition of 10 .mu.g/mL L. major lysate, soluble Leishmania antigens (prepared as described in Example 6) or L-Rack. These results indicate that M15 and soluble Leishmania antigens, but not L-Rack, are potent stimulators of IFN-.gamma. production in patient PBMC, but not in PBMC obtained from uninfected individuals. Thus, M15 and soluble Leishmania antigens elicit a dominant Th1 cytokine profile in both mice and humans infected with Leishmania.

Detailed Description Text (140):
Comparison of Proliferation Stimulated by Leishmania Antigens

Detailed Description Text (143):
FIG. 16 illustrates the proliferation observed after addition of 10 .mu.g/mL or 20 .mu.g/mL of each of the following antigens to a lymph node culture prepared as described in Example 7: SLA, Ldp23, LbeIF4A, Lbhsp83, and M15. The level of proliferation without the addition of antigen is also shown. Data are represented as mean cpm. These results demonstrate that a variety of leishmanial antigens are capable of stimulatory lymph node cell proliferation from Leishmania-infected mice.

Detailed Description Text (144):
FIGS. 17 and 18 illustrate the proliferation observed in human PBMC preparations from Leishmania-immune and uninfected individuals following the addition of 10 .mu.g/mL M15 and soluble Leishmania antigens, respectively. These values are compared to the proliferation observed following the addition of culture medium, L. major lysate or L-Rack. The results show that M15 and soluble Leishmania antigens stimulate proliferation in Leishmania-immune PBMC, but not in PBMC obtained from uninfected individuals, demonstrating that M15 and soluble antigens (but not L-Rack) are recognized by PBMC from individuals immune to Leishmania due to a previous infection.

Detailed Description Text (147):
This Example illustrates the preparation of two soluble Leishmania antigens, Lmspla and Lmsp9a.

Detailed Description Text (150):
Anti E. coli antibody reactivities were removed from the rabbit sera by pre-adsorbing on nitrocellulose filters containing lysed E. coli. Adsorbed sera were evaluated by Western blot analysis using 10 .mu.g Leishmania promastigote lysate (lane 1) and 1 .mu.g soluble L. major antigen mixture (lane 2). As shown in FIG. 20, the rabbit sera was found to be reactive with seven dominant antigens of the soluble L. major antigen mixture with molecular weights ranging from 18 to >200 kDa. A four times longer exposure of the same blot revealed three additional immunoreactive species with molecular weights less than 18 kDa. The same sera reacted with approximately 10 antigens of the promastigote lysate, but with a pattern significantly different from that observed with the soluble L. major antigens (FIG. 20). This is suggestive of potential post-translational modification

of the same antigen before (intracellular localization) and after secretion/shedding. Such modifications may include cleavage of a leader sequence and/or the addition of carbohydrate molecules to the secreted/shed antigens.

Detailed Description Text (151):
The rabbit sera described above was subsequently used to screen an L. major cDNA expression library prepared from L. major promastigote RNA using the unidirectional Lambda ZAP (uni-ZAP) kit (Stratagene) according to the manufacturer's protocol. A total of 70,000 pfu of the amplified cDNA library was screened with the rabbit sera at a 1:250 dilution. Nineteen positive clones were confirmed in the tertiary screening. The phagemid were excised and DNA from each of the 19 clones was sequenced using a Perkin Elmer/Applied Biosystems Division automated sequencer Model 373A. All 19 clones were found to represent two distinct sequences, referred to as Lmspla and Lmsp9a. The determined cDNA sequences for Lmspla and Lmsp9a are provided in SEQ ID NO: 19 and 21, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 20 and 22, respectively.

Detailed Description Text (155):
Southern blot analysis of genomic DNA from L. major (Friedlander strain) digested with a panel of restriction enzymes (lanes 1 to 7) and six other Leishmania species of different geographic locations digested with PstI (lanes 8 to 13) using the full-length cDNA insert of Lmspla, demonstrated that Lmspla is present in all the species characterized with a high degree of conservation (FIG. 22). This suggests evolutionary significance for the maintenance of Lmspla and the existence of homologous species among all the Leishmania species.

Detailed Description Text (156):
The remaining two cDNA clones isolated from the soluble L. major antigen mixture represent identical sequences (referred to as Lmsp9a; SEQ ID NO: 21), suggesting that the two copies resulted from amplification of the primary library. Sequencing of the Lmsp9a cDNA revealed that the clone does not contain the full length 5' sequence since it is lacking both the spliced leader and 5' untranslated sequences. The 3' end of the cDNA contains a poly A stretch, as would be expected for a Leishmania mRNA. Of the predicted translated sequence (SEQ ID NO: 22), 34 of the 201 amino acids (17%) represent cysteine residues. Comparison of the predicted protein sequence with those of known proteins as described above, revealed some homology with other cysteine rich proteins such as the major surface trophozoite antigen of Giardia lamblia and furin proteases.

Detailed Description Text (159):
This Example illustrates the preparation and characterization of the Leishmania antigen MAPS-1A (SEQ ID NO: 24).

Detailed Description Text (161):
One of these clones, referred to herein as MAPS-1A, was found to be full-length. Comparison of the cDNA and deduced amino acid sequences for MAPS-1A (SEQ ID Nos: 23 and 24, respectively) with known sequences in the gene bank using the DNA STAR system revealed no significant homologies to known Leishmania sequences, although some sequence similarity was found to a group of proteins, known as thiol-specific antioxidants, found in other organisms.

Detailed Description Text (162):
Recombinant MAPS-1A protein having an amino-terminal HIS-Tag was prepared using a high level E. coli expression system and recombinant protein was purified by affinity chromatography as described in Example 1. Southern blot analysis of genomic DNA from L. major digested with a panel of restriction enzymes, seven other Leishmania species digested with PstI, and two other infectious-disease pathogens (T. cruzi and T. brucei), using the full length insert of MAPS-1A, demonstrated that MAPS-1A is present in all eight Leishmania species tested (FIG. 23). Northern blot analysis of L. major promastigote aid amastigote RNAs indicated that MAPS-1A is constitutively expressed.

Detailed Description Text (164):
The ability of recombinant MAPS-1A to stimulate cell proliferation was investigated

as follows. PBMC from 3 L. braziliensis-infected patients having active mucosal leishmaniasis, from 4 patients post kala-azar infection (previously infected with L. chagasi and/or L. donovani) and from 3 uninfected-individuals were prepared as described above in Example 7. The ability of MAPS-1A to stimulate proliferation of these PBMC was determined as described in Example 8 above. As shown in FIG. 24, significant levels of MAPS-1A specific PBMC proliferation were seen in 2 of the 7 Leishmania patients.

Detailed Description Text (167):
Immunoreactivity of Soluble Leishmania Antigens with Sera from Leishmania-Infected Patents

Detailed Description Text (171):
As shown in FIG. 26, approximately 50% of the samples from human leishmaniasis patients showed reactivities with recombinant MAPS-1A substantially above background. FIG. 27 shows the reactivity of MAPS-1A with increasing dilutions of sera from BALB/c mice previously administered either (i) saline solution; (ii) the adjuvant B. pertussis; (iii) soluble Leishmania antigens plus B. pertussis; (iv) live L. major promastigotes; or (v) soluble Leishmania antigens plus B. pertussis followed by live L. major promastigotes (as described below in Example 12). Considerably higher absorbances were seen with sera from mice infected with live L. major promastigotes and with mice infected with live L. major promastigotes following immunization with soluble Leishmania antigens plus B. pertussis, than with sera from the other three groups of mice, indicating that anti-MAPS-1A antibody titers increase following Leishmania infection.

Detailed Description Text (173):
Use of Leishmania Antigens for Vaccination Against Leishmania Infection

Detailed Description Text (174):
This example illustrates the effectiveness of Leishmania antigens in conferring protection against disease in the experimental murine leishmaniasis model system. For a discussion of the murine leishmaniasis model system see, for example, Reiner et al. Annu. Rev. Immunol., 13:151-77, 1995.

Detailed Description Text (175):
The effectiveness of (i) crude soluble Leishmania antigens, (ii) MAPS-1A, and (iii) a mixture of Ldp23, LbeIF4A and M15, as vaccines against Leishmania infection was determined as follows. BALB/c mice (5 per group) were immunized intra-peritoneally three times at biweekly intervals with either (i) 30 .mu.g crude soluble Leishmania antigens, (ii)20 .mu.g MAPS-1A or (iii) a mixture containing 10 .mu.g each of LeIF, Ldp23 and M15, together with 100 .mu.g of the adjuvant C. parvum. Two control groups were immunized with either saline or C. parvum alone. Two weeks after the last immunization, the mice were challenged with 2.times.15.sup.5 late-log phase promastigotes of L. major. Infection was monitored weekly by measurement of footpad swelling. The amount of footpad swelling seen in mice immunized with either crude soluble Leishmania antigens, a mixture of Ldp23, LbeiF4A and M15 (FIG. 28), or MAPS-1A (FIG. 29) was significantly less than that seen in mice immunized with C. parvum alone. These results demonstrate that the Leishmania antigens of the present invention are effective in conferring protection against Leishmania infection.

Detailed Description Text (178):
This example illustrates the isolation of seven soluble Leishmania antigen genes from an L. major genomic DNA library.

Detailed Description Text (179):
An L. major genomic DNA expression library was prepared from L. major promastigotes using the unidirectional Lambda ZAP (uni-ZAP) kit (Stratagene) according to the manufacturer's protocol. This library was screened with a high titer rabbit sera raised against L. major soluble antigens, as described above in Example 9. Seven positive clones were identified. The phagemid were excised and DNA from each of the seven clones was sequenced using a Perkin Elmer/Applied Biosystems Division automated sequencer Model 373A. The DNA sequences for these antigens, referred to as LmgSP1, LmgSP3, LmgSP5, LmgSP8, LmgSP9, LmgSP13, LmgSP19, are provided in SEQ ID

NO:29-35, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 36-42, respectively. LmgSP13 was found to contain a 39 amino acid repeat sequence shown in SEQ ID NO:43.

Detailed Description Text (182):
The reactivity of recombinant LmgSP9 with sera from patients with visceral leishnianiasis, (from both Sudan and Brazil) and from normal donors was evaluated by ELISA as described above. The absorbance values were compared with those obtained using the known Leishmania antigen K39 described above, with L. chagasi lysate being employed as a positive control. Representative results of these assays are provided below in Table 2, wherein all the patients from Brazil and those from the Sudan designated as "VL" were inflicted with visceral leishmaniasis. The results demonstrated that LmgSP9 specifically detects antibody in most individuals with visceral leishmaniasis, regardless of geographical location. In several cases, the absorbance values of the antibody reactivity to LmgSP9 were comparable to that observed with K39. In addition, LmgSP9 detected several cases of leishmaniasis that were not detected using K39. These results indicate that LmgSP9 can be used to complement the reactivity of K39.

Detailed Description Text (188):
This example illustrates the preparation of five soluble Leishmania antigen genes from an L. chagasi genomic DNA library.

Detailed Description Text (189):
An L. chagasi genomic DNA expression library was prepared from L. chagasi promastigotes using the unidirectional Lambda ZAP (uni-ZAP) kit (Stratagene) according to the manufacturer's protocol. This library was screened with a high titer rabbit sera raised against L. major soluble antigens, as described above in Example 9. Five positive clones were identified. The phagemid were excised and DNA from each of the Five clones was sequenced using a Perkin Elmer/Applied Biosystems Division automated sequencer Model 373A. The DNA sequences for these antigens, referred to as LcgSP1, LcgSP3, LcgSP4, LcgSP8, and LcgSP10 are provided in SEQ ID NO:44-48, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO:49-53, respectively.

Detailed Description Text (195):
Leishmania-specific CD4+ T cell lines were derived from the PBMC of an individual who tested positive in a leishmania skin test but had no clinical history of disease. These T cell lines were used to screen a L. major amastigote cDNA expression library prepared as described in Example 1. Immunoreactive clones were isolated and sequenced as described above. The determined cDNA sequences for the 8 isolated clones referred to as 1G6-34, 1E6-44, 4A5-63, 1B11-39, 2A10-37, 4G2-83, 4H6-41, 8G3-100 are provided in SEQ ID NO: 72-79. respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 80-87, respectively. The cDNA sequences provided for 1E6-44, 2A10-37. 4G2-83, 4H6-41 and 8G3-100 are believe to represent partial clones. All of these clones were shown to stimulate T cell proliferation.

Detailed Description Text (201):
Use of Leishmania Antigens Plus Adjuvant for Vaccination Against Leishmania Infection

Detailed Description Text (202):
This example illustrates the effectiveness of recombinant Leishmania antigens, M15 and MAPS, plus an adjuvant, IL-12, in conferring protection against disease in the experimental murine leishmaniasis model system. For discussion of the murine leishmaniasis model system see, for example, Reiner et al., Annu. Rev. Immunol., 13:151-77, 1995. The effectiveness of M15 and MAPS in combination with IL-12, as vaccine against Leishmania infection was determined as follows: BALB/c mice (5 per group) were immunized subcutaneously in the left footpad, twice (3 weeks apart) with the 10 .mu.g of the individual antigens mixed with 1 .mu.g of IL-12. As controls, three separate groups of mice were immunized with soluble leishmania lysate antigens (SLA) plus IL-12, with IL-12 alone or with PBS. Three weeks after the last immunization the mice were infected in the right footpad with

2.times.10.sup.5 promastigote forms of L. major (stationary phase). Footpad swelling was then measured weekly. Results are expressed in FIG. 31 and clearly indicate that the mice immunized with either M15 or MAPS and IL-12 were greatly protected against the infection; whereas mice immunized with IL-12 alone did not show protection from infection. The protection induced by these antigens was as efficient or better than that induced by SLA+IL-12, a regimen known to induce good protection against leishmaniasis in this animal model (Afonso, L. C. C., T. M. Scharton, L. Q. Vieira, M. Wysocka, G. Trinchieri, and P. Scott. 1994. The adjuvant effect of interieukin-12 in a vaccine against Leishniania major. Science 263:235-237). The same pattern of protection described above, was obtained i.e., M15, MAPS, and SLA, induced protection against L. major infection when C. parvum instead of IL-12 was used as adjtivant (Example 12). These results demonstrate that both M15 and MAPS recombinant antigens induce excellent protection against L. major infection in the BALB/c model of human leishmaniasis. In addition, both antigens induced protection when tested in two different adjuvant formulations, (e.g., IL-12 and C. parvim.) This finding is of high significance because it demonstrates that immunity to leishmaniasis can be induced by the specific antigens delivered in adjuvants that are suitable for human use.

Detailed Description Text (204):
Use of Leishmania DNA for Vaccination Against Leishmania Infection

Detailed Description Text (205):
This example illustrates the effectiveness of Leishmania DNA in conferring protection against disease in the experimental murine leishmaniasis model system. For discussion of the murine leishmaniasis model system see, for example, Reiner et al., Annu. Rev. Immunol., 13:151-77, 1995. The protection properties of the recombinant antigens was tested by immunizing mice with naked DNA containing the corresponding M15 and MAPS genes. The DNA construct used was the pcDNA3.1 vector (Invitrogen) containing a CMV promotor. BALB/c mice (5 per group) were injected in the left footpad three times (3 weeks apart) with 100 .mu.g of the indicated naked DNA preparations. Mice were bled before and after the immunizations to monitor the development of specific immune response. The antibody response was evaluated by ELISA. Specific anti-M15 and anti-MAPS IgG2a antibodies were detected after the second immunization in the sera of the mice immunized with the respective naked DNA. The presence of specific antibodies indicates that the DNA immunization resulted in the production of specific protein antigen. Three weeks after the last immunization, the mice were then challenged in the right footpad with 2.times.10.sup.5 promastigote forms of L. major (stationary phase). Footpad swelling was then measured weekly thereafter. Results are expressed in FIG. 32 and clearly indicated that, again, mice immunized with naked DNA containing either the M15 or MAPS genes were greatly protected against the infection with L. major. These results demonstrate that both M15 and MAPS genes induce excellent protection against L. major infection in the BALB/c model of human leishmaniasis.

Detailed Description Text (207):
Preparation and Characterization of Leishmania Fusion Proteins

Detailed Description Text (208):
Fusion proteins comprising the Leishmania antigens MAPS-1A (SEQ ID NO: 24), M15 (SEQ ID NO: 2), Lbhsp83 (SEQ ID NO: 6) and LbeIF4A (SEQ ID NO: 10) were prepared as follows.

Detailed Description Text (214):
Use of Leishmania Fusion Proteins Plus Adjuvant for Vaccination Against Leishmania Infection

Detailed Description Text (215):
The ability of the Leishmania fusion proteins MAPS1A-M15 (referred to as the diFusion) and MAPS1A-M15-LbeIF4A (referred to as the triFusion), plus adjuvant, to confer protection against disease in the experimental murine leishmaniasis model system was examined as follows.

Detailed Description Paragraph Table (1):

h e b b g e e e f c e e ge

TABLE 1 In vitro Proliferation of PMBC from L. braziliensis-infected Individuals in Response to Lbhsp83 Mean [.sup.3 H] thymidine Group and incorporation [10.sup.3 cpm (SD)], SI with: Patient Lysate Lbhsp83a Lbhsp83b ML I 41.3, (1.3), 294 32.5, (6.6), 221 46.7, (1.4), 318 II 44.2, (0.5), 104 20, (3.7), 47 36.7, (0.76), 86 III 27.4, (1.5), 150 8.1, (1.7), 44 9.9, (0.32), 54 IV 52.7, (3.3), 138 54.1, (6.2), 142 32.0, (1.3), 84 V 140.6, (7.6), 308 151.8, (57), 333 150.4, (7.9), 331 VI 15.8, (1.8), 20 21.3, (4.4), 28 14.4, (1.3), 19 VII 300.1, (9.4), 1634 102.1, (7.6), 558 41.7, (4.9), 228 CL I 0.26, (0.0), 1.5 0.57, (0.3), 3.3 0.43, (0.17), 3.3 II 55.63, (8.6), 218 0.42, (0.0), 1.6 0.8, (0.14), 3.2 III 0.39, (0.5), 4.0 3.4, (0.5), 9 2.6, (0.9), 6.6 IV 19.14, (1.3), 87 7.17, (0.6), 32 5.9, (0.9), 27 V 0.32, (0.2), 3.0 1.47, (0.5), 14 0.3, (0.1), 3.0 VI 0.77, (0.1), 4.7 1.44, (0.2), 9 1.3, (0.6), 8.0 VII 4.01, (1.0), 2.0 60.3, (8.5), 15 66.7, (3.9), 16.6 Self-healing CL I 19.7, (4.4), 94 61.3, (4.6), 293 5.0, (2.0), 24 II 0.6, (0.1), 6.5 7.0, (2.0), 79 1.2, (0.8), 13 III 59.6, (7.1), 519 49.4, (3.1), 429 21.4, (3.7), 186 IV 0.2, (0.1), 1.6 13.1, (1.7), 108 0.6, (0.1), 5 V 27.1, (2.0), 225 6.3, (2.6), 52 3.0, (1.5), 25 VI 130.3, (14), 340 28.2, (2.9), 74 7.7, (3.8), 20 Control (uninfected) I 0.19, (0.0), 1.4 0.18, (0.0), 1.3 0.40, (0.16), 2.8 II 0.31, (0.1), 1.7 0.19, (0.0), 1.0 0.27, (0.0), 1.5 III 0.44, (0.2), 4.1 0.48, (0.1), 5.0 0.51, (0.2), 5.2 IV 0.4, (0.1), 3.2 0.52, (0.2), 5.1 0.50, (0.1), 5.0

Detailed Description Paragraph Table (2):

TABLE 2 REACTIVITY OF LMGSP9 WITH SERA FROM LEISHMANIA PATIENTS Patient No. L. chagasi lysate K39 LmgSP9 Sudanese samples: B19 1.067 0.306 0.554 B25 1.884 3.435 0.974 B43 1.19 3.225 0.86 B47 2.405 2.892 0.375 B50 0.834 0.748 0.432 B58 0.921 0.235 0.92 B63 1.291 0.303 0.764 B70 0.317 0.089 3.056 VL4 1.384 3.035 2.965 VL11 0.382 0.144 0.142 VL12 0.277 0.068 0.098 VL13 0.284 0.12 0.194 Brazilian samples: 105 3.508 3.53 0.374 106 2.979 3.373 2.292 107 2.535 3.444 0.46 109 1.661 3.415 3.319 111 3.595 3.537 0.781 112 2.052 3.469 0.63 113 3.352 3.429 0.963 114 2.316 3.437 1.058 115 2.073 3.502 1.186 116 3.331 3.461 0.96 Normal Donors: 129 0.157 0.104 0.08 130 0.195 0.076 0.095 131 0.254 0.134 0.086 132 0.102 0.035 0.043

Detailed Description Paragraph Table (3):

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1800 cgagaacgac aaggccgtga aggacctcgt cttcctgctc ttcgacacgt cgctgctcac 1860
gtccggcttc cagctggatg accccaccgg ctacgccgag cgcatcaacc gcatgatcaa 1920 gctcggcctg
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Asn 20 25 30 Gly Ile Gly Met Thr Lys Ala Asp Leu Val Asn Asn Leu Gly Thr Ile 35 40
45 Ala Arg Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Glu Ala Gly Gly 50 55 60 Asp Met
Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr 65 70 75 80 Leu Val Ala Asp
Arg Val Thr Val Val Ser Lys Asn Asn Ser Asp Glu 85 90 95 Ala Tyr Trp Glu Ser Ser
Ala Gly Gly Thr Phe Thr Ile Thr Ser Val 100 105 110 Gln Glu Ser Asp Met Lys Arg Gly
Thr Ser Thr Thr Leu His Leu Lys 115 120 125 Glu Asp Gln Gln Glu Tyr Leu Glu Glu Arg
Arg Val Lys Glu Leu Ile

Detailed Description Paragraph Table (4):

130 135 140 Lys Lys His Ser Glu Phe Ile Gly Tyr Asp Ile Glu Leu Met Val Glu 145 150
155 160 Lys Thr Ala Glu Lys Glu Val Thr Asp Glu Asp Glu Glu Glu Asp Glu 165 170 175
Ser Lys Lys Lys Ser Cys Gly Asp Glu Gly Glu Pro Lys Val Glu Glu 180 185 190 Val Thr
Glu Gly Gly Glu Asp Lys Lys Lys Lys Thr Lys Lys Val Lys 195 200 205 Glu Val Lys Lys
Thr Tyr Glu Val Lys Asn Lys His Lys Pro Leu Trp 210 215 220 Thr Arg Asp Thr Lys Asp
Val Thr Lys Glu Glu Tyr Ala Ala Phe Tyr 225 230 235 240 Lys Ala Ile Ser Asn Asp Trp
Glu Asp Thr Ala Ala Thr Lys His Phe 245 250 255 Ser Val Glu Gly Gln Leu Glu Phe Arg
Ala Ile Ala Phe Val Pro Lys 260 265 270 Arg Ala Pro Phe Asp Met Phe Glu Pro Asn Lys
Lys Arg Asn Asn Ile 275 280 285 Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Asn Cys
Glu Asp Leu 290 295 300 Cys Pro Asp Trp Leu Gly Phe Val Lys Gly Val Val Asp Ser Glu

h e b b g e e e f c e e ge

Asp 305 310 315 320 Leu Pro Leu Asn Ile Ser Arg Glu Asn Leu Gln Gln Asn Lys Ile Leu
325 330 335 Lys Val Ile Arg Lys Asn Ile Val Lys Lys Cys Leu Glu Leu Phe Glu 340 345
350 Glu Ile Ala Glu Asn Lys Glu Asp Tyr Lys Gln Phe Tyr Glu Gln Phe 355 360 365 Gly
Lys Asn Ile Lys Leu Gly Ile His Glu Asp Thr Ala Asn Arg Lys 370 375 380 Lys Leu Met
Glu Leu Leu Arg Phe Tyr Ser Thr Glu Ser Gly Glu Glu 385 390 395 400 Met Thr Thr Leu
Lys Asp Tyr Val Thr Arg Met Lys Pro Glu Gln Lys 405 410 415 Ser Ile Tyr Tyr Ile Thr
Gly Asp Ser Lys Lys Lys Leu Glu Ser Ser 420 425 430 Pro Phe Ile Glu Lys Ala Arg Arg
Cys Gly Leu Glu Val Leu Phe Met 435 440 445 Thr Glu Pro Ile Asp Glu Tyr Val Met Gln
Gln Val Lys Asp Phe Glu 450 455 460 Asp Lys Lys Phe Ala Cys Leu Thr Lys Glu Gly Val
His Phe Glu Glu 465 470 475 480 Ser Glu Glu Glu Lys Lys Gln Arg Glu Glu Lys Lys Ala
Ala Cys Glu 485 490 495 Lys Leu Cys Lys Thr Met Lys Glu Val Leu Gly Asp Lys Val Glu
Lys 500 505 510 Val Thr Val Ser Glu Arg Leu Leu Thr Ser Pro Cys Ile Leu Val Thr 515
520 525 Ser Glu Phe Gly Trp Ser Ala His Met Glu Gln Ile Met Arg Asn Gln 530 535 540
Ala Leu Arg Asp Ser Ser Met Ala Gln Tyr Met Val Ser Lys Lys Thr 545 550 555 560 Met
Glu Val Asn Pro Asp His Pro Ile Ile Lys Glu Leu Arg Arg Arg 565 570 575 Val Glu Ala
Asp Glu Asn Asp Lys Ala Val Lys Asp Leu Val Phe Leu 580 585 590 Leu Phe Asp Thr Ser
Leu Leu Thr Ser Gly Phe Gln Leu Asp Asp Pro 595 600 605 Thr Gly Tyr Ala Glu Arg Ile
Asn Arg Met Ile Lys Leu Gly Leu Ser 610 615 620 Leu Asp Glu Glu Glu Glu Glu Val Ala
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cgcctggagg ccatgcacga ggccgagcag 300 gcccgctccc aggccctcga ggaggcagcg cgtctccgcg
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gagcaggccc gcgtccaggc cctcgaggag 780 gcagcgcgtc tccgcgcgga gctggaggcg gccgaggagg
cggcccgcct ggatgtcatg 840 cacgagggcg agcaggcccg tgtccaggcc ctcgaggagg cggcccgcct
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960 ctggaggctg aggaggagga aaaagatgag cggccggcga cgtcgagcta cagcgaggag 1020
tgcaaagggc gactgctatc gagggcgcgg ccggatccgc ggaggccgct gccgcggccg 1080 ttcattggga
tgtcactgtt ggaggatgtg gagaagagta ttctcattgt ggacgggctc 1140 tacagggatg ggccggcgta
ccagacgggc atccgcctcg gggatgtcct cttgcgtatc 1200 gcgggggttt acgtggattc aatagcgaag
gcgaggcagg tggtcgatgc gcgttgccgc 1260 tgcggctgcg tcgttcccgt gacgctggcg acgaagatga
accagcagta cagcgtggct 1320 ctgtatatca tgacggtgga tccgcagcac aacgacaagc ccttttttt
tgatgtgcac 1380 atccaccacc gcatcgagag ctcgcacatg gggaagaagg cgcagtggat ggaagttctt
1440 gagagcccat ccgtatcttc ggctgccacc acccctctcg tgccgctctt gcgtgagccg 1500
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gcgcgcgcag gtcggtcagc tcagaaagtg agcgaccgcg cgggtcctct 1620 agcgtggcta tggcggagga
ggcgatcgcg ctggcgccgc aagggtatac cccacccaac 1680 caagtgcgcg gccgtagttg acgtctctgt
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Leu Arg Ala 35 40 45 Glu Leu Glu Glu Ala Glu Glu Ala Ala Arg Leu Asp Val Met His
Ala 50 55 60 Ala Glu Gln Ala Arg Val Gln Ala Leu Glu Glu Ala Ala Arg Leu Arg 65 70
75 80 Ala Glu Leu Glu Ala Ala Glu Glu Ala Ala Arg Leu Glu Ala Met His 85 90 95 Glu
Ala Glu Gln Ala Arg Ser Gln Ala Leu Glu Glu Ala Ala Arg Leu 100 105 110 Arg Ala Glu
Leu Glu Glu Ala Glu Glu Ala Ala Arg Leu Asp Val Met 115 120 125 His Ala Ala Glu Gln
Ala Arg Val Gln Ala Leu Glu Glu Ala Ala Arg 130 135 140 Leu Arg Ala Glu Leu Glu Glu
Ala Glu Glu Ala Ala Arg Leu Glu Ala 145 150 155 160 Met His Glu Ala Glu Gln Ala Arg
Ser Gln Ala Leu Glu Glu Ala Ala 165 170 175 Arg Leu Arg Ala Glu Leu Glu Ala Ala Glu
Glu Ala Ala Arg Leu Asp 180 185 190 Val Met His Glu Ala Glu Gln Ala Arg Val Gln Ala
Leu Glu Glu Ala 195 200 205 Ala Arg Leu Asp Val Met His Glu Ala Glu Gln Ala Arg Val
Gln Ala 210 215 220 Leu Glu Glu Ala Ala Arg Leu Arg Ala Glu Leu Glu Ala Ala Glu Glu
225 230 235 240 Ala Ala Arg Leu Asp Val Met His Glu Ala Glu Gln Ala Arg Val Gln 245
250 255 Ala Leu Glu Glu Ala Ala Arg Leu Arg Ala Glu Leu Glu Ala Ala Glu 260 265 270

h e b b g e e e f c e e ge

Glu Ala Ala Arg Leu Asp Val Met His Glu Gly Glu Gln Ala Arg Val 275 280 285 Gln Ala
Leu Glu Glu Ala Ala Arg Leu Glu Ala Met His Glu Ala Glu 290 295 300 Gln Ala Arg Ser
Gln Ala Leu Glu Glu Ala Ala Arg Leu Cys Ala Glu 305 310 315 320 Leu Glu Ala Glu Glu
Glu Glu Lys Asp Glu Arg Pro Ala Thr Ser Ser 325 330 335 Tyr Ser Glu Glu Cys Lys Gly
Arg Leu Leu Ser Arg Ala Arg Pro Asp 340 345 350 Pro Arg Arg Pro Leu Pro Arg Pro Phe
Ile Gly Met Ser Leu Leu Glu 355 360 365 Asp Val Glu Lys Ser Ile Leu Ile Val Asp Gly
Leu Tyr Arg Asp Gly 370 375 380 Pro Ala Tyr Gln Thr Gly Ile Arg Leu Gly Asp Val Leu
Leu Arg Ile 385 390 395 400 Ala Gly Val Tyr Val Asp Ser Ile Ala Lys Ala Arg Gln Val
Val Asp 405 410 415 Ala Arg Cys Arg Cys Gly Cys Val Val Pro Val Thr Leu Ala Thr Lys
420 425 430 Met Asn Gln Gln Tyr Ser Val Ala Leu Tyr Ile Met Thr Val Asp Pro 435 440
445 Gln His Asn Asp Lys Pro Phe Phe Phe Asp Val His Ile His His Arg 450 455 460 Ile
Glu Ser Ser His Met Gly Lys Lys Ala Gln Trp Met Glu Val Leu 465 470 475 480 Glu Ser
Pro Ser Val Ser Ser Ala Ala Thr Thr Pro Leu Val Pro Leu 485 490 495 Leu Arg Glu Pro
Thr Pro Arg Arg Gly Ser Glu Leu Gln Ser Ser Ala 500 505 510 Arg Ser Ala Phe Val Ala
Thr Ser Tyr Phe Ser Ser Ala Arg Arg Ser 515 520 525 Val Ser Ser Glu Ser Glu Arg Pro
Arg Gly Ser Ser Ser Val Ala Met 530 535 540 Ala Glu Glu Ala Ile Ala Leu Ala Pro Gln
Gly Tyr Thr Pro Pro Asn 545 550 555 560 Gln Val Arg Gly Arg Ser 565 <200> SEQUENCE
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tcgacgacca gcccggcgtc 180 cgcccgatcc cgtccttcga tgacatgccg ttgcaccaga accttctgcg
cggcatctac 240 tcgtacggct tcgagaaacc gtccagcatc cagcagcgcg ccatcgcccc cttcacgcgc
300 ggcggcgaca tcatcgcgca ggcgcagtcc ggtaccggca agacgggcgc cttctccatc 360
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tggccctgca gacggcggag gtgatcagcc gcatcggcga gttcctgtcg 480 aacagcgcga agttctgtga
gacctttgtg ggtggcacgc gcgtgcagga tgacctgcgc 540 aagctgcagg ctggcgtcgt cgtcgccgtg
gggacgccgg gccgcgtgtc cgacgtgatc 600 aagcgcggcg cgctgcgcac cgagtccctg cgcgtgctgg
tgctcgacga ggctgatgag 660 atgctgtctc agggcttcgc ggatcagatt tacgagatct tccgcttcct
gccgaaggac 720 atccaggtcg cgctcttctc cgccacgatg ccggaggagg tgctggagct gacaaagaag
780 ttcatgcgcg accccgtacg cattctcgtg aagcgcgaga gcctgacgct ggagggcatc 840
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ccatcgcgca gtccgtcatc ttcgccaaca cccgccgcaa ggtggactgg 960 atcgccgaga agctgaatca
gagcaaccac accgtcagca gcatgcacgc cgagatgccc 1020 aagagcgacc gcgagcgcgt catgaacacc
ttccgcagcg gcagctcccg cgtgctcgta 1080 acgaccgacc tcgtggcccg cggcatcgac gtgcaccacg
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ccgctacggc 1200 gtaaagggtg ttgccatcaa cttcgtgacg gagaaagacg tggagctgct gcacgagatc
1260 gaggggcact accacacgca gatcgatgag ctcccggtgg actttgccgc ctacctcggc 1320
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cacgcgaacg atagtaaggg cgtgcggcgg cgttcccctc ctcctgccag 1440 cggcccccct ccgcagcgct
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Asn Leu Leu Arg Gly Ile Tyr Ser Tyr Gly Phe Glu Lys 35 40 45 Pro Ser Ser Ile Gln
Gln Arg Ala Ile Ala Pro Phe Thr Arg Gly Gly 50 55 60 Asp Ile Ile Ala Gln Ala Gln
Ser Gly Thr Gly Lys Thr Gly Ala Phe 65 70 75 80 Ser Ile Gly Leu Leu Gln Arg Leu Asp
Phe Arg His Asn Leu Ile Gln 85 90 95 Gly Leu Val Leu Ser Pro Thr Arg Glu Leu Ala
Leu Gln Thr Ala Glu 100 105 110 Val Ile Ser Arg Ile Gly Glu Phe Leu Ser Asn Ser Ala
Lys Phe Cys 115 120 125 Glu Thr Phe Val Gly Gly Thr Arg Val Gln Asp Asp Leu Arg Lys
Leu 130 135 140 Gln Ala Gly Val Val Val Ala Val Gly Thr Pro Gly Arg Val Ser Asp 145
150 155 160 Val Ile Lys Arg Gly Ala Leu Arg Thr Glu Ser Leu Arg Val Leu Val 165 170
175 Leu Asp Glu Ala Asp Glu Met Leu Ser Gln Gly Phe Ala Asp Gln Ile 180 185 190 Tyr
Glu Ile Phe Arg Phe Leu Pro Lys Asp Ile Gln Val Ala Leu Phe 195 200 205 Ser Ala Thr
Met Pro Glu Glu Val Leu Glu Leu Thr Lys Lys Phe Met 210 215 220 Arg Asp Pro Val Arg
Ile Leu Val Lys Arg Glu Ser Leu Thr Leu Glu 225 230 235 240 Gly Ile Lys Gln Phe Phe
Ile Ala Val Glu Glu Glu His Lys Leu Asp 245 250 255 Thr Leu Met Asp Leu Tyr Glu Thr
Val Ser Ile Ala Gln Ser Val Ile

Detailed Description Paragraph Table (5):
260 265 270 Phe Ala Asn Thr Arg Arg Lys Val Asp Trp Ile Ala Glu Lys Leu Asn 275 280
285 Gln Ser Asn His Thr Val Ser Ser Met His Ala Glu Met Pro Lys Ser 290 295 300 Asp

h e b b g e e e f c e e ge

Arg Glu Arg Val Met Asn Thr Phe Arg Ser Gly Ser Ser Arg Val 305 310 315 320 Leu Val Thr Thr Asp Leu Val Ala Arg Gly Ile Asp Val His His Val 325 330 335 Asn Ile Val Ile Asn Phe Asp Leu Pro Thr Asn Lys Glu Asn Tyr Leu 340 345 350 His Arg Ile Gly Arg Gly Gly Arg Tyr Gly Val Lys Gly Val Ala Ile 355 360 365 Asn Phe Val Thr Glu Lys Asp Val Glu Leu Leu His Glu Ile Glu Gly 370 375 380 His Tyr His Thr Gln Ile Asp Glu Leu Pro Val Asp Phe Ala Ala Tyr 385 390 395 400 Leu Gly Glu <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 11 <211> LENGTH: 12 <212> TYPE: PRT <213> ORGANISM: Leishmania donovani <220> FEATURE: <221> NAME/KEY: VARIANT <222> LOCATION: (1)...(5) <223> OTHER INFORMATION: Xaa = any amino acid <400> SEQUENCE: 11 Xaa Gln Xaa Pro Gln Xaa Val Phe Asp Glu Xaa Xaa 1 5 10 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 12 <211> LENGTH: 26 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Sense PCR pri mer <400> SEQUENCE: 12 ggaattcccc ncagctngtn ttcgac 26 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 13 <211> LENGTH: 5 <212> TYPE: PRT <213> ORGANISM: Leishmania donovani <400> SEQUENCE: 13 Lys Val Phe Asp Glu 1 5 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 14 <211> LENGTH: 30 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR primer <400> SEQUENCE: 14 ggatccatgg tcaagtccca ctacatctgc 30 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 15 <211> LENGTH: 33 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR primer <400> SEQUENCE: 15 gaattcagac cggatagaaa taagccaatg aaa 33 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 16 <211> LENGTH: 701 <212> TYPE: PRT <213> ORGANISM: Leishmania amozonensis <400> SEQUENCE: 16 Met Thr Glu Thr Phe Ala Phe Gln Ala Glu Ile Asn Gln Leu Met Ser 1 5 10 15 Leu lle Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Asp 20 25 30 Val Ile Ser Asn Ala Ser Asp Ala Cys Asp Lys Ile Arg Tyr Gln Ser 35 40 45 Leu Thr Asp Pro Ala Val Leu Gly Asp Ala Thr Arg Leu Cys Val Arg 50 55 60 Val Val Pro Asp Lys Glu Asn Lys Thr Leu Thr Val Glu Asp Asn Gly 65 70 75 80 Ile Gly Met Thr Lys Ala Asp Leu Val Asn Asn Leu Gly Thr Ile Ala 85 90 95 Arg Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Glu Ala Gly Ala Asp 100 105 110 Met Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu 115 120 125 Val Ala Asp Arg Val Thr Val Thr Ser Lys Asn Asn Ser Asp Glu Val 130 135 140 Tyr Val Trp Glu Ser Ser Ala Gly Gly Thr Phe Thr Ile Thr Ser Ala 145 150 155 160 Pro Glu Ser Asp Met Lys Leu Pro Ala Arg Ile Thr Leu His Leu Lys 165 170 175 Glu Asp Gln Leu Glu Tyr Leu Glu Ala Arg Arg Leu Lys Glu Leu Ile 180 185 190 Lys Lys His Ser Glu Phe Ile Gly Tyr Asp Ile Glu Leu Met Val Glu 195 200 205 Lys Thr Thr Glu Lys Glu Val Thr Asp Glu Asp Glu Glu Glu Ala Lys 210 215 220 Lys Ala Asp Glu Asp Gly Glu Glu Pro Lys Val Glu Glu Val Thr Glu 225 230 235 240 Gly Glu Glu Asp Lys Lys Lys Lys Thr Lys Lys Val Lys Glu Val Thr 245 250 255 Lys Glu Tyr Glu Val Gln Asn Lys His Lys Pro Leu Trp Thr Arg Asp 260 265 270 Pro Lys Asp Val Thr Lys Glu Glu Tyr Ala Ala Phe Tyr Lys Ala Ile 275 280 285 Ser Asn Asp Trp Glu Asp Pro Pro Ala Thr Lys His Phe Ser Val Glu 290 295 300 Gly Gln Leu Glu Phe Arg Ala Ile Met Phe Val Pro Lys Arg Ala Pro 305 310 315 320 Phe Asp Met Leu Glu Pro Asn Lys Lys Arg Asn Asn Ile Lys Leu Tyr 325 330 335 Val Arg Arg Val Phe Ile Met Asp Asn Cys Glu Asp Leu Cys Pro Asp 340 345 350 Trp Leu Gly Phe Val Lys Gly Val Val Asp Ser Glu Asp Leu Pro Leu 355 360 365 Asn Ile Ser Arg Glu Asn Leu Gln Gln Asn Lys Ile Leu Lys Val Ile 370 375 380 Arg Lys Asn Ile Val Lys Lys Cys Leu Glu Met Phe Glu Glu Val Ala 385 390 395 400 Glu Asn Lys Glu Asp Tyr Lys Gln Phe Tyr Glu Gln Phe Gly Lys Asn 405 410 415 Ile Lys Leu Gly Ile His Glu Asp Thr Ala Asn Arg Lys Lys Leu Met 420 425 430 Glu Leu Leu Arg Phe Tyr Ser Thr Glu Ser Gly Glu Val Met Thr Thr 435 440 445 Leu Lys Asp Tyr Val Thr Arg Met Lys Ala Glu Gln Asn Ser Ile Tyr 450 455 460 Tyr Ile Thr Gly Asp Ser Lys Lys Lys Leu Glu Ser Ser Pro Phe Ile 465 470 475 480 Glu Gln Ala Lys Arg Arg Gly Phe Glu Val Leu Phe Met Thr Glu Pro 485 490 495 Tyr Asp Glu Tyr Val Met Gln Gln Val Lys Asp Phe Glu Asp Lys Lys 500 505 510 Phe Ala Cys Leu Thr Lys Glu Gly Val His Phe Glu Glu Ser Glu Glu 515 520 525 Glu Lys Lys Gln Arg Glu Glu Glu Lys Ala Thr Cys Glu Lys Leu Cys 530 535 540 Lys Thr Met Lys Glu Val Leu Gly Asp Lys Val Glu Lys Val Thr Val 545 550 555 560 Ser Glu Arg Leu Ser Thr Ser Pro Cys Ile Leu Val Thr Ser Glu Phe 565 570 575 Gly Trp Ser Ala His Met Glu Gln Met Met Arg Asn Gln Ala Leu Arg 580 585 590 Asp Ser Ser Met Ala Gln Tyr Met Met Ser Lys Lys Thr Met Glu Leu 595 600 605 Asn Pro Lys His Pro Ile Ile Lys Glu Leu Arg Arg Arg Val Glu Ala 610 615 620 Asp Glu Asn Asp Lys Ala Val Lys Asp Leu Val Phe Leu Leu Phe Asp 625 630 635 640 Thr Ser Leu Leu Thr Ser Gly Phe Gln Leu Glu Asp Pro Thr Tyr Ala 645 650 655 Glu Arg Ile Asn Arg Met Ile Lys Leu Gly Leu Ser Leu Asp Glu Glu 660 665 670 Glu Glu Glu Glu Ala 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Ser Asn Ala Ser Asp Ala Cys Asp Lys Ile Arg Tyr Gln Ser 35 40 45 Leu Thr Asn Gln
Ala Val Leu Gly Asp Glu Ser His Leu Arg Ile Arg 50 55 60 Val Val Pro Asp Lys Ala
Asn Lys Thr Leu Thr Val Glu Asp Thr Gly 65 70 75 80 Ile Gly Met Thr Lys Ala Glu Leu
Val Asn Asn Leu Gly Thr Ile Ala 85 90 95 Arg Ser Gly Thr Lys Ala Phe Met Glu Ala
Leu Glu Ala Gly Gly Asp 100 105 110 Met Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr
Ser Ala Tyr Leu 115 120 125 Val Ala Asp Arg Val Thr Val Val Ser Lys Asn Asn Asp Asp
Glu Ala 130 135 140 Tyr Thr Trp Glu Ser Ser Ala Gly Gly Thr Phe Thr Val Thr Pro Thr
145 150 155 160 Pro Asp Cys Asp Leu Lys Arg Gly Thr Arg Ile Val Leu His Leu Lys 165
170 175 Glu Asp Gln Gln Glu Tyr Leu Glu Glu Arg Arg Leu Lys Asp Leu Ile 180 185 190
Lys Lys His Ser Glu Phe Ile Gly Tyr Asp Ile Glu Leu Met Val Glu 195 200 205 Lys Ala
Thr Glu Lys Glu Val Thr Asp Glu Asp Glu Asp Glu Ala Ala 210 215 220 Ala Thr Lys Asn
Glu Glu Gly Glu Glu Pro Lys Val Glu Glu Val Lys 225 230 235 240 Asp Asp Ala Glu Glu
Gly Glu Lys Lys Lys Lys Thr Lys Lys Val Lys 245 250 255 Glu Val Thr Gln Glu Phe Val
Val Gln Asn Lys His Lys Pro Leu Trp 260 265 270 Thr Arg Asp Pro Lys Asp Val Thr Lys
Glu Glu Tyr Ala Ala Phe Tyr 275 280 285 Lys Ala Ile Ser Asn Asp Trp Glu Glu Pro Leu
Ser Thr Lys His Phe 290 295 300 Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Ile Leu Phe
Val Pro Lys 305 310 315 320 Arg Ala Pro Phe Asp Met Phe Glu Pro Ser Lys Lys Arg Asn
Asn Ile 325 330 335 Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Asn Cys Glu Asp Leu
340 345 350 Cys Pro Glu Trp Leu Ala Phe Val Arg Gly Val Val Asp Ser Glu Asp 355 360
365 Leu Pro Leu Asn Ile Ser Arg Glu Asn Leu Gln Gln Asn Lys Ile Leu 370 375 380 Lys
Val Ile Arg Lys Asn Ile Val Lys Lys Ala Leu Glu Leu Phe Glu 385 390 395 400 Glu Ile
Ala Glu Asn Lys Glu Asp Tyr Lys Lys Phe Tyr Glu Gln Phe 405 410 415 Gly Lys Asn Val
Lys Leu Gly Ile His Glu Asp Ser Ala Asn Arg Lys 420 425 430 Lys Leu Met Glu Leu Leu
Arg Phe His Ser Ser Glu Ser Gly Glu Asp 435 440 445 Met Thr Thr Leu Lys Asp Tyr Val
Thr Arg Met Lys Glu Gly Gln Lys 450 455 460 Cys Ile Tyr Tyr Val Thr Gly Asp Ser Lys
Lys Lys Leu Glu Thr Ser 465 470 475 480 Pro Phe Ile Glu Gln Ala Arg Arg Arg Gly Phe
Glu Val Leu Phe Met 485 490 495 Thr Glu Pro Ile Asp Glu Tyr Val Met Gln Gln Val Lys
Asp Phe Glu 500 505 510 Asp Lys Lys Phe Ala Cys Leu Thr Lys Glu Gly Val His Phe Glu
Glu 515 520 525 Thr Glu Glu Glu Lys Lys Gln Arg Glu Glu Glu Lys Thr Ala Tyr Glu 530
535 540 Arg Leu Cys Lys Ala Met Lys Asp Val Leu Gly Asp Lys Val Glu Lys 545 550 555
560 Val Val Val Ser Glu Arg Leu Ala Thr Ser Pro Cys Ile Leu Val Thr 565 570 575 Ser
Glu Phe Gly Trp Ser Ala His Met Glu Gln Ile Met Arg Asn Gln 580 585 590 Ala Leu Arg
Asp Ser Ser Met Ser Ala Tyr Met Met Ser Lys Lys Thr 595 600 605 Met Glu Ile Asn Pro
Ala His Pro Ile Val Lys Glu Leu Lys Arg Arg 610 615 620 Val Glu Ala Asp Glu Asn Asp
Lys Ala Val Lys Asp Leu Val Tyr Leu 625 630 635 640 Leu Phe Asp Thr Ala Leu Leu Thr
Ser Gly Phe Thr Leu Asp Asp Pro 645 650 655 Thr Ser Tyr Ala Glu Arg Ile His Arg Met
Ile Lys Leu Gly Leu Ser 660 665 670 Leu Asp Asp Glu Asp Asn Gly Asn Glu Glu Ala Glu
Pro Ala Ala Ala 675 680 685

Detailed Description Paragraph Table (6):

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Arg Glu Leu 35 40 45 Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser
Leu 50 55 60 Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu 65 70
75 80 Ile Pro Asn Lys Gln Asp Arg Ala Leu Thr Ile Val Asp Thr Gly Ile 85 90 95 Gly
Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys 100 105 110 Ser Gly Thr
Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile 115 120 125 Ser Met Ile Gly Gln
Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val 130 135 140 Ala Glu Lys Val Thr Val Ile
Thr Lys His Asn Asp Asp Glu Gln Tyr 145 150 155 160 Ala Trp Glu Ser Ser Ala Gly Gly
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Glu Tyr Leu Asn Phe 370 375 380 Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn
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Leu Val 50 55 60 Lys Tyr Phe Ser Ser Gly Pro Ile Val Cys Met Val Trp Glu Gly Lys 65
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Lys Ser Ile Ala Arg Ser Tyr Gly Val Leu Glu Glu 115 120 125 Ser Gln Gly Val Ala Tyr Arg Gly Leu Phe Ile Ile Asp Pro Arg Gly 130 135 140 Met Val Arg Gln Ile Thr Val Asn Asp Met Pro Val Gly Arg Asn Val 145 150 155 160 Glu Glu Ala Leu Arg Leu Leu Glu Ala Leu Gln Phe Val Glu Lys His 165 170 175 Gly Glu Val Cys Pro Ala Asn Trp Lys Lys Gly Ala Pro Thr Met Lys 180 185 190 Pro Glu Pro Lys Ala Ser Val Glu Gly Tyr Phe Ser Lys Gln 195 200 205 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 27 <211> LENGTH: 51 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR primer <400> SEQUENCE: 27 caattacata tgcatcacca tcaccatcac atgtcctgcg gtaacgccaa g 51 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 28 <211> LENGTH: 31 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR primer <400> SEQUENCE: 28 catggaattc ttactgcttg ctgaagtatc c 31 <200> SEQUENCE CHARACTERISTICS: <210> SEQ ID NO 29 <211> LENGTH: 520 <212> TYPE: DNA 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Detailed Description Paragraph Table (10):
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Asp Gly Ala Cys Val Arg Cys Gln Glu Pro 100 105 110 Asn Cys Phe Ser Cys Asp Ser Asp
Ala Asn Lys Cys Thr Gln Cys Ala 115 120 125 Pro Asn Tyr Tyr Leu Thr Pro Leu Leu Thr
Cys Ser Pro Val Ala Cys 130 135 140 Asn Ile Glu His Cys Met Gln Cys Asp Pro Gln Thr
Pro Ser Arg Cys 145 150 155 160 Gln Glu Cys Val Ser Pro Tyr Val Val Asp Ser Tyr Asp
Gly Leu Cys 165 170 175 Arg Leu Ser Asp Ala Cys Ser Val Pro Asn Cys Lys Lys Cys Glu
Thr 180 185 190 Gly Thr Ser Arg Leu Cys Ala Glu Cys Asp Thr Gly Tyr Ser Leu Ser 195
200 205 Ala Asp Ala Thr Ser Cys Ser Ser Pro Thr Thr Gln Pro Cys Glu Val 210 215 220
Glu His Cys Asn Thr Cys Val Asn Gly Asp Ser Thr Arg Cys Ala Tyr 225 230 235 240 Cys
Asn Thr Gly Tyr Tyr Val Ser Asp Gly Lys Cys Lys Ala Met Gln 245 250 255 Gly Cys Tyr
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Detailed Description Paragraph Table (12):

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Gln 50 55 60 Gly Leu Val His Val Asp Asn His Pro Arg Arg Asp Gly Lys Tyr Pro 65 70 75 80 Ala Gly Phe Met Asp Val Val Glu Ile Pro Lys Thr Gly Asp Arg Phe 85 90 95 Arg Leu Met Tyr Asp Val Lys Gly Arg Phe Ala Leu Val Asn Leu Ser 100 105 110 Glu Ala Glu Ala Gln Ile Lys Leu Met Lys Val Val Asn Leu Tyr Thr 115 120 125 Ala Thr Gly Arg Val Pro Val Ala Val Thr His Asp Gly His Arg Ile 130 135 140 Arg Tyr Pro Asp Pro His Thr Ser Ile Gly Asp Thr Ile Val Tyr Asn 145 150 155 160 Val Lys Glu Lys Lys Cys Val Asp Leu Ile Lys Asn Arg Gln Gly Lys 165 170 175 Ala Val Ile Val Thr Gly Gly Ala Asn Arg Gly Arg Ile Gly Glu Ile 180 185 190 Val Lys Val Glu Cys His Pro Gly Ala Phe Asn Ile Ala His Leu Lys 195 200 205 Asp Ala Ser Gly Ala Glu Phe Ala Thr Arg Ala Ala Asn Ile Phe Val 210 215 220 Ile Gly Lys Asp Leu Asn Asn Leu Gln Val Thr Val Pro Lys Gln Gln 225 230 235 240 Gly Leu Arg Met Asn Val Ile Gln Glu Arg Glu Glu Arg Leu Ile Ala 245 250 255 Ala Glu Ala Arg Lys Asn Ala Pro Ala Arg Gly Ala Arg Arg Ala Arg 260 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Phe Thr Phe Val Cys Pro Thr Glu Val Ile 50 55 60 Ala Phe Ser Asp Ser Val Ser Arg Phe Asn Glu Leu Asn Cys Glu Val 65 70 75 80 Leu Ala Cys Ser Ile Asp Ser Glu Tyr Ala His Leu Gln Trp Thr Leu 85 90 95 Gln Asp Arg Lys Lys Gly Gly Leu Gly Thr Met Ala Ile Pro Met Leu 100 105 110 Ala Asp Lys Thr Lys Ser Ile Ala Arg Ser Tyr Gly Val Leu Glu Glu 115 120 125 Ser Gln Gly Val Ala Tyr Arg Gly Leu Phe Ile Ile Asp Pro His Gly 130 135 140 Met Leu Arg Gln Ile Thr Val Asn Asp Met Pro Val Gly Arg Ser Val 145 150 155 160 Glu Glu Val Leu Arg Leu Leu Glu Ala Phe Gln Phe Val Glu Lys His 165 170 175 Gly Glu Val Cys Pro Ala Asn Trp Lys Lys Gly Ala Pro Thr Met Lys 180 185 190 Pro Glu Pro Asn Ala Ser Val Glu Gly Tyr Phe Ser Lys Gln Gly Ser 195 200 205 Met Asp Ala Thr Glu Leu Lys Asn Lys Gly Asn Glu Glu Phe Ser Ala 210 215 220 Gly Arg Tyr Val Glu Ala Val Asn Tyr Phe Ser Lys Ala Ile Gln Leu 225 230 235 240 Asp Glu Gln Asn Ser Val Leu Tyr Ser Asn Arg Ser Ala Cys Phe Ala 245 250 255 Ala Met Gln Lys Tyr Lys Asp Ala Leu Asp Asp Ala Asp Lys Cys Ile 260 265 270 Ser Ile Lys Pro Asn Trp Ala Lys Gly Tyr Val Arg Arg Gly Ala Ala 275 280 285 Leu His Gly Met Arg Arg Tyr Asp Asp Ala Ile Ala Ala Tyr Glu Lys 290 295 300 Gly Leu Lys Val Asp Pro Ser Asn Ser Gly Cys Ala Gln Gly Val Lys 305 310 315 320 Asp Val Gln Val Ala Lys Ala Arg Glu Ala Arg Asp Pro Ile Ala Arg 325 330 335 Val Phe Thr Pro Glu Ala Phe Arg Lys Ile Gln Glu Asn Pro Lys Leu 340 345 350 Ser Leu Leu Met Leu Gln Pro Asp Tyr Val Lys Met Val Asp Thr Val 355 360 365 Ile Arg Asp Pro Ser Gln Gly Arg Leu Tyr Met Glu Asp Gln Arg Phe 370 375 380 Ala Leu Thr Leu Met Tyr Leu Ser Gly Met Lys Ile Pro Asn Asp Gly 385 390 395 400 Asp Gly Glu Glu Glu Glu Arg Pro Ser Ala Lys Ala Ala Glu Thr Ala 405 410 415 Lys Pro Lys Glu Glu Lys Pro Leu Thr Asp Asn Glu Lys Glu Ala Leu 420 425 430 Ala Leu Lys Glu Glu Gly Asn Lys Leu Tyr Leu Ser Lys Lys Phe Glu 435 440 445 Glu Ala Leu Thr Lys Tyr Gln Glu Ala Gln Val Lys Asp Pro Asn Asn 450 455 460 Thr Leu Tyr Ile Leu Asn Val Ser Ala Val Tyr Phe Glu Gln Gly Asp 465 470 475 480 Tyr Asp Lys Cys Ile Ala Glu Cys Glu His Gly Ile Glu His Gly Arg 485 490 495 Glu Asn His Cys Asp Tyr Thr Ile Ile Ala Lys Leu Met Thr Arg Asn 500 505 510 Ala Leu Cys Leu Gln Arg Gln Arg Lys Tyr Glu Ala Ala Ile Asp Leu 515 520 525 Tyr Lys Arg Ala Leu Val Glu Trp Arg Asn Pro Asp Thr Leu Lys Lys 530 535 540 Leu Thr Glu Cys Glu Lys Glu His Gln Lys Ala Val Glu Glu Ala Tyr 545 550 555 560 Ile Asp Pro Glu Ile Ala Lys Gln Lys Lys Asp Glu Gly Asn Gln Tyr 565 570 575 Phe Lys Glu Asp Lys Phe Pro Glu Ala Val Ala Ala Tyr Thr Glu Ala 580 585 590 Ile Lys Arg Asn Pro Ala Glu His Thr Ser Tyr Ser Asn Arg Ala Ala 595 600 605 Ala Tyr Ile Lys Leu Gly Ala Phe Asn Asp Ala Leu Lys Asp Ala Glu 610 615 620 Lys Cys Ile Glu Leu Lys Pro Asp Phe Val Lys Gly Tyr Ala Arg Lys 625 630 635 640 Gly His Ala Tyr Phe Trp Thr Lys Gln Tyr Asn Arg Ala Leu Gln Ala 645 650 655 Tyr Asn Glu Gly Leu Lys Val Asp Pro Ser Asn Ala Asp Cys Lys Asp 660 665 670 Gly Arg Tyr Arg Thr Ile Met Lys Ile Gln Glu Met Ala Ser Gly Gln 675 680 685 Ser Ala Asp Gly Asp Glu Ala Ala Arg Arg Ala Met Asp Asp Pro Glu 690 695 700 Ile Ala Ala Ile Met Gln Asp Ser Tyr Met Gln Leu Val Leu Lys Glu 705 710 715 720 Met Gln Asn Asp Pro Thr Arg Ile Gln Glu Tyr Met Lys Asp Ser Gly 725 730 735 Ile Ser Ser Lys Ile Asn Lys Leu Ile Ser Ala Gly Ile Ile Arg Phe 740 745 750 Gly Gln Glu Phe Met Ala Gln Asn Asp Lys Ile Ala Pro Gln Asp Gln 755 760 765 Asp Ser Phe Leu Asp Asp Gln Pro Gly Val Arg Pro Ile Pro Ser Phe 770 775 780 Asp Asp Met Pro Leu His Gln Asn Leu Leu Arg Gly Ile Tyr Ser Tyr 785 790 795 800 Gly Phe Glu Lys Pro Ser Ser Ile Gln Gln Arg Ala Ile Ala Pro Phe 805 810 815 Thr Arg Gly Gly Asp Ile Ile Ala Gln Ala Gln Ser Gly Thr Gly Lys 820 825 830 Thr Gly Ala Phe Ser Ile Gly Leu Leu Gln Arg Leu Asp Phe Arg His 835 840 845 Asn Leu Ile Gln Gly Leu Val Leu Ser Pro Thr Arg Glu Leu Ala Leu 850 855 860 Gln Thr Ala Glu Val Ile Ser Arg Ile Gly Glu Phe Leu Ser Asn Ser 865 870 875 880 Ser Lys Phe Cys Glu Thr Phe Val Gly Gly Thr Arg Val Gln Asp Asp 885 890 895 Leu Arg Lys Leu Gln Ala Gly Val Ile Val Ala Val Gly Thr Pro Gly 900 905 910 Arg Val Ser Asp Val Ile Lys Arg Gly Ala Leu Arg Thr Glu Ser Leu 915 920 925 Arg Val Leu Val Leu Asp Glu Ala Asp Glu Met Leu Ser Gln Gly Phe 930 935 940 Ala Asp Gln Ile Tyr Glu Ile Phe Arg Phe Leu Pro Lys Asp Ile Gln 945 950 955

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Ala Phe Tyr Lys Ala Ile Ser Asn Asp Trp Glu Asp Pro Ala 995 1000 1005 Ala Thr Lys
His Phe Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Ile 1010 1015 1020 Ala Phe Val Pro
Lys Arg Ala Pro Phe Asp Met Phe Glu Pro Asn Lys 1025 1030 1035 1040 Lys Arg Asn Asn
Ile Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp 1045 1050 1055 Asn Cys Glu Asp Leu
Cys Pro Asp Trp Leu Gly Phe Val Lys Gly Val 1060 1065 1070 Val Asp Ser Glu Asp Leu
Pro Leu Asn Ile Ser Arg Glu Asn Leu Gln 1075 1080 1085 Gln Asn Lys Ile Leu Lys Val
Ile Arg Lys Asn Ile Val Lys Lys Cys 1090 1095 1100 Leu Glu Leu Phe Glu Glu Ile Ala
Glu Asn Lys Glu Asp Tyr Lys Gln 1105 1110 1115 1120 Phe Tyr Glu Gln Phe Gly Lys Asn
Ile Lys Leu Gly Ile His Glu Asp 1125 1130 1135 Thr Ala Asn Arg Lys Lys Leu Met Glu
Leu Leu Arg Phe Tyr Ser Thr 1140 1145 1150 Glu Ser Gly Glu Glu Met Thr Thr Leu Lys
Asp Tyr Val Thr Arg Met 1155 1160 1165 Lys Pro Glu Gln Lys Ser Ile Tyr Tyr Ile Thr
Gly Asp Ser Lys Lys 1170 1175 1180 Lys Leu Glu Ser Ser Pro Phe Ile Glu Lys Ala Arg
Arg Cys Gly Leu 1185 1190 1195 1200 Glu Val Leu Phe Met Thr Glu Pro Ile Asp Glu Tyr
Val Met Gln Gln 1205 1210 1215 Val Lys Asp Phe Glu Asp Lys Lys Phe Ala Cys Leu Thr
Lys Glu Gly 1220 1225 1230 Val His Phe Glu Glu Ser Glu Glu Glu Lys Lys Gln Arg Glu
Glu Lys 1235 1240 1245 Lys Ala Ala Cys Glu Lys Leu Cys Lys Thr Met Lys Glu Val Leu
Gly 1250 1255 1260 Asp Lys Val Glu Lys Val Thr Val Ser Glu Arg Leu Ser Thr Ser Pro
1265 1270 1275 1280 Cys Ile Leu Val Thr Ser Glu Phe Gly Trp Ser Ala His Met Glu Gln
1285 1290 1295 Ile Met Arg Asn Gln Ala Leu Arg Asp Ser Ser Met Ala Gln Tyr Met 1300
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1325 Glu Leu Arg Arg Arg Val Glu Ala Asp Glu Asn Asp Lys Ala Val Lys 1330 1335 1340
Asp Leu Val Phe Leu Leu Phe Asp Thr Ser Leu Leu Thr Ser Gly Phe 1345 1350 1355 1360
Gln Leu Asp Asp Pro Thr Gly Tyr Ala Glu Arg Ile Asn Arg Met Ile 1365 1370 1375 Lys
Leu Gly Leu Ser Leu Asp Glu Glu Glu Glu Glu Val Ala Glu Ala 1380 1385 1390 Pro Pro
Ala Glu Ala Ala Pro Ala Glu Val Thr Ala Gly Thr Ser Ser 1395 1400 1405 Met Glu Gln
Val Asp Asp Ile Met Ala Gln Asn Asp Lys Ile Ala Pro 1410 1415 1420 Gln Asp Gln Asp
Ser Phe Leu Asp Asp Gln Pro Gly Val Arg Pro Ile 1425 1430 1435 1440 Pro Ser Phe Asp
Asp Met Pro Leu His Gln Asn Leu Leu Arg Gly Ile 1445 1450 1455 Tyr Ser Tyr Gly Phe
Glu Lys Pro Ser Ser Ile Gln Gln Arg Ala Ile 1460 1465 1470 Ala Pro Phe Thr Arg Gly
Gly Asp Ile Ile Ala Gln Ala Gln Ser Gly 1475 1480 1485 Thr Gly Lys Thr Gly Ala Phe
Ser Ile Gly Leu Leu Gln Arg Leu Asp 1490 1495 1500 Phe Arg His Asn Leu Ile Gln Gly
Leu Val Leu Ser Pro Thr Arg Glu 1505 1510 1515 1520 Leu Ala Leu Gln Thr Ala Glu Val
Ile Ser Arg Ile Gly Glu Phe Leu 1525 1530 1535 Ser Asn Ser Ser Lys Phe Cys Glu Thr
Phe Val Gly Gly Thr Arg Val 1540 1545 1550 Gln Asp Asp Leu Arg Lys Leu Gln Ala Gly
Val Ile Val Ala Val Gly 1555 1560 1565 Thr Pro Gly Arg Val Ser Asp Val Ile Lys Arg
Gly Ala Leu Arg Thr 1570 1575 1580 Glu Ser Leu Arg Val Leu Val Leu Asp Glu Ala Asp
Glu Met Leu Ser 1585 1590 1595 1600 Gln Gly Phe Ala Asp Gln Ile Tyr Glu Ile Phe Arg
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Phe Thr Phe Val Cys Pro Thr Glu Val Ile 50 55 60 Ala Phe Ser Asp Ser Val Ser Arg
Phe Asn Glu Leu Asn Cys Glu Val 65 70 75 80 Leu Ala Cys Ser Ile Asp Ser Glu Tyr Ala
His Leu Gln Trp Thr Leu 85 90 95 Gln Asp Arg Lys Lys Gly Gly Leu Gly Thr Met Ala
Ile Pro Met Leu 100 105 110 Ala Asp Lys Thr Lys Ser Ile Ala Arg Ser Tyr Gly Val Leu
Glu Glu 115 120 125 Ser Gln Gly Val Ala Tyr Arg Gly Leu Phe Ile Ile Asp Pro His Gly
130 135 140 Met Leu Arg Gln Ile Thr Val Asn Asp Met Pro Val Gly Arg Ser Val 145 150
155 160 Glu Glu Val Leu Arg Leu Leu Glu Ala Phe Gln Phe Val Glu Lys His 165 170 175
Gly Glu Val Cys Pro Ala Asn Trp Lys Lys Gly Ala Pro Thr Met Lys 180 185 190 Pro Glu
Pro Asn Ala Ser Val Glu Gly Tyr Phe Ser Lys Gln Gly Ser 195 200 205 Met Asp Ala Thr
Glu Leu Lys Asn Lys Gly Asn Glu Glu Phe Ser Ala 210 215 220 Gly Arg Tyr Val Glu Ala
Val Asn Tyr Phe Ser Lys Ala Ile Gln Leu 225 230 235 240 Asp Glu Gln Asn Ser Val Leu
Tyr Ser Asn Arg Ser Ala Cys Phe Ala 245 250 255 Ala Met Gln Lys Tyr Lys Asp Ala Leu
Asp Asp Ala Asp Lys Cys Ile 260 265 270 Ser Ile Lys Pro Asn Trp Ala Lys Gly Tyr Val
Arg Arg Gly Ala Ala 275 280 285 Leu His Gly Met Arg Arg Tyr Asp Asp Ala Ile Ala Ala
Tyr Glu Lys 290 295 300 Gly Leu Lys Val Asp Pro Ser Asn Ser Gly Cys Ala Gln Gly Val
Lys

Detailed Description Paragraph Table (15):
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h e b b g e e e f c e e ge

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Ser Leu Leu Met Leu Gln Pro Asp Tyr Val Lys Met Val Asp Thr Val 355 360 365 Ile Arg
Asp Pro Ser Gln Gly Arg Leu Tyr Met Glu Asp Gln Arg Phe 370 375 380 Ala Leu Thr Leu
Met Tyr Leu Ser Gly Met Lys Ile Pro Asn Asp Gly 385 390 395 400 Asp Gly Glu Glu Glu
Glu Arg Pro Ser Ala Lys Ala Ala Glu Thr Ala 405 410 415 Lys Pro Lys Glu Glu Lys Pro
Leu Thr Asp Asn Glu Lys Glu Ala Leu 420 425 430 Ala Leu Lys Glu Glu Gly Asn Lys Leu
Tyr Leu Ser Lys Lys Phe Glu 435 440 445 Glu Ala Leu Thr Lys Tyr Gln Glu Ala Gln Val
Lys Asp Pro Asn Asn 450 455 460 Thr Leu Tyr Ile Leu Asn Val Ser Ala Val Tyr Phe Glu
Gln Gly Asp 465 470 475 480 Tyr Asp Lys Cys Ile Ala Glu Cys Glu His Gly Ile Glu His
Gly Arg 485 490 495 Glu Asn His Cys Asp Tyr Thr Ile Ile Ala Lys Leu Met Thr Arg Asn
500 505 510 Ala Leu Cys Leu Gln Arg Gln Arg Lys Tyr Glu Ala Ala Ile Asp Leu 515 520
525 Tyr Lys Arg Ala Leu Val Glu Trp Arg Asn Pro Asp Thr Leu Lys Lys 530 535 540 Leu
Thr Glu Cys Glu Lys Glu His Gln Lys Ala Val Glu Glu Ala Tyr 545 550 555 560 Ile Asp
Pro Glu Ile Ala Lys Gln Lys Lys Asp Glu Gly Asn Gln Tyr 565 570 575 Phe Lys Glu Asp
Lys Phe Pro Glu Ala Val Ala Ala Tyr Thr Glu Ala 580 585 590 Ile Lys Arg Asn Pro Ala
Glu His Thr Ser Tyr Ser Asn Arg Ala Ala 595 600 605 Ala Tyr Ile Lys Leu Gly Ala Phe
Asn Asp Ala Leu Lys Asp Ala Glu 610 615 620 Lys Cys Ile Glu Leu Lys Pro Asp Phe Val
Lys Gly Tyr Ala Arg Lys 625 630 635 640 Gly His Ala Tyr Phe Trp Thr Lys Gln Tyr Asn
Arg Ala Leu Gln Ala 645 650 655 Tyr Asn Glu Gly Leu Lys Val Asp Pro Ser Asn Ala Asp
Cys Lys Asp 660 665 670 Gly Arg Tyr Arg Thr Ile Met Lys Ile Gln Glu Met Ala Ser Gly
Gln 675 680 685 Ser Ala Asp Gly Asp Glu Ala Ala Arg Arg Ala Met Asp Asp Pro Glu 690
695 700 Ile Ala Ala Ile Met Gln Asp Ser Tyr Met Gln Leu Val Leu Lys Glu 705 710 715
720 Met Gln Asn Asp Pro Thr Arg Ile Gln Glu Tyr Met Lys Asp Ser Gly 725 730 735 Ile
Ser Ser Lys Ile Asn Lys Leu Ile Ser Ala Gly Ile Ile Arg Phe 740 745 750 Gly Gln Glu
Phe Ser Leu Thr Asp Pro Ala Val Leu Gly Glu Glu Thr 755 760 765 His Leu Arg Val Arg
Val Val Pro Asp Lys Ala Asn Lys Thr Leu Thr 770 775 780 Val Glu Asp Asn Gly Ile Gly
Met Thr Lys Ala Asp Leu Val Asn Asn 785 790 795 800 Leu Gly Thr Ile Ala Arg Ser Gly
Thr Lys Ala Phe Met Glu Ala Leu 805 810 815 Glu Ala Gly Gly Asp Met Ser Met Ile Gly
Gln Phe Gly Val Gly Phe 820 825 830 Tyr Ser Ala Tyr Leu Val Ala Asp Arg Val Thr Val
Val Ser Lys Asn 835 840 845 Asn Ser Asp Glu Ala Tyr Val Trp Glu Ser Ser Ala Gly Gly
Thr Phe 850 855 860 Thr Ile Thr Ser Val Pro Glu Ser Asp Met Lys Arg Gly Thr Arg Ile
865 870 875 880 Thr Leu His Leu Lys Glu Asp Gln Gln Glu Tyr Leu Glu Glu Arg Arg 885
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Glu Asp Glu Ser Lys Lys Lys Ser Cys Gly Asp Glu Gly Glu 930 935 940 Pro Lys Val Glu
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Asn Asp Trp Glu Asp Pro Ala 995 1000 1005 Ala Thr Lys His Phe Ser Val Glu Gly Gln
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Lys Cys 1090 1095 1100 Leu Glu Leu Phe Glu Glu Ile Ala Glu Asn Lys Glu Asp Tyr Lys
Gln 1105 1110 1115 1120 Phe Tyr Glu Gln Phe Gly Lys Asn Ile Lys Leu Gly Ile His Glu
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1160 1165 Lys Pro Glu Gln Lys Ser Ile Tyr Tyr Ile Thr Gly Asp Ser Lys Lys 1170 1175
1180 Lys Leu Glu Ser Ser Pro Phe Ile Glu Lys Ala Arg Arg Cys Gly Leu 1185 1190 1195
1200 Glu Val Leu Phe Met Thr Glu Pro Ile Asp Glu Tyr Val Met Gln Gln 1205 1210 1215
Val Lys Asp Phe Glu Asp Lys Lys Phe Ala Cys Leu Thr Lys Glu Gly 1220 1225 1230 Val
His Phe Glu Glu Ser Glu Glu Glu Lys Lys Gln Arg Glu Glu Lys 1235 1240 1245 Lys Ala
Ala Cys Glu Lys Leu Cys Lys Thr Met Lys Glu Val Leu Gly 1250 1255 1260 Asp Lys Val
Glu Lys Val Thr Val Ser Glu Arg Leu Ser Thr Ser Pro 1265 1270 1275 1280 Cys Ile Leu
Val Thr Ser Glu Phe Gly Trp Ser Ala His Met Glu Gln 1285 1290 1295 Ile Met Arg Asn
Gln Ala Leu Arg Asp Ser Ser Met Ala Gln Tyr Met 1300 1305 1310 Val Ser Lys Lys Thr
Met Glu Val Asn Pro Asp His Pro Ile Ile Lys 1315 1320 1325 Glu Leu Arg Arg Arg Val
Glu Ala Asp Glu Asn Asp Lys Ala Val Lys 1330 1335 1340 Asp Leu Val Phe Leu Leu Phe
Asp Thr Ser Leu Leu Thr Ser Gly Phe 1345 1350 1355 1360 Gln Leu Asp Asp Pro Thr Gly
Tyr Ala Glu Arg Ile Asn Arg Met Ile 1365 1370 1375 Lys Leu Gly Leu Ser Leu Asp Glu
Glu Glu Glu Glu Val Ala Glu Ala 1380 1385 1390 Pro Pro Ala Glu Ala Ala Pro Ala Glu
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Previous Doc Next Doc Go to Doc#